MAR 30 1938

Individuality and Responsibility Have a Value in Establishing the Standing of the Pharmacist in Professional Activities. Pharmacy Is Known by Its Service and the Pharmacist by His Personality and Devotion to Pharmaceutical Duties.

Vol. XXVII, No. 2 FEBRUARY, 1938

JOURNAL OF THE AMERICAN PHARMACEUTICAL ASSOCIATION

TRADE MARK

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THE 86th ANNUAL MEETING OF THE AMERICAN PHARMACEUTICAL ASSOCIATION WILL BE HELD IN MINNEAPOLIS, MINN., Hotel Nicollet, August 22–27, 1938.

The 1938 Meetings of the American Association of Colleges of Pharmacy, the National Association of Boards of Pharmacy, Conference of Pharmaceutical Association Secretaries, of the Pharmaceutical Law Enforcement Officials and the Plant Science Seminar will also be held in Minneapolis, Minn.

Entered as second-class Matter, January 23, 1917, at the Post Office at Easton, Pa., under the act of March 3, 1879. Acceptance for mailing at a special rate of postage provided for in section 1103. Act of October 3, 1917; authorized July 10, 1918.

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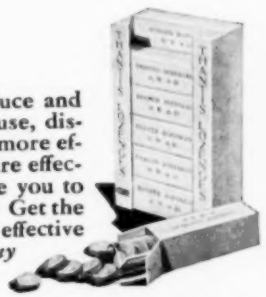

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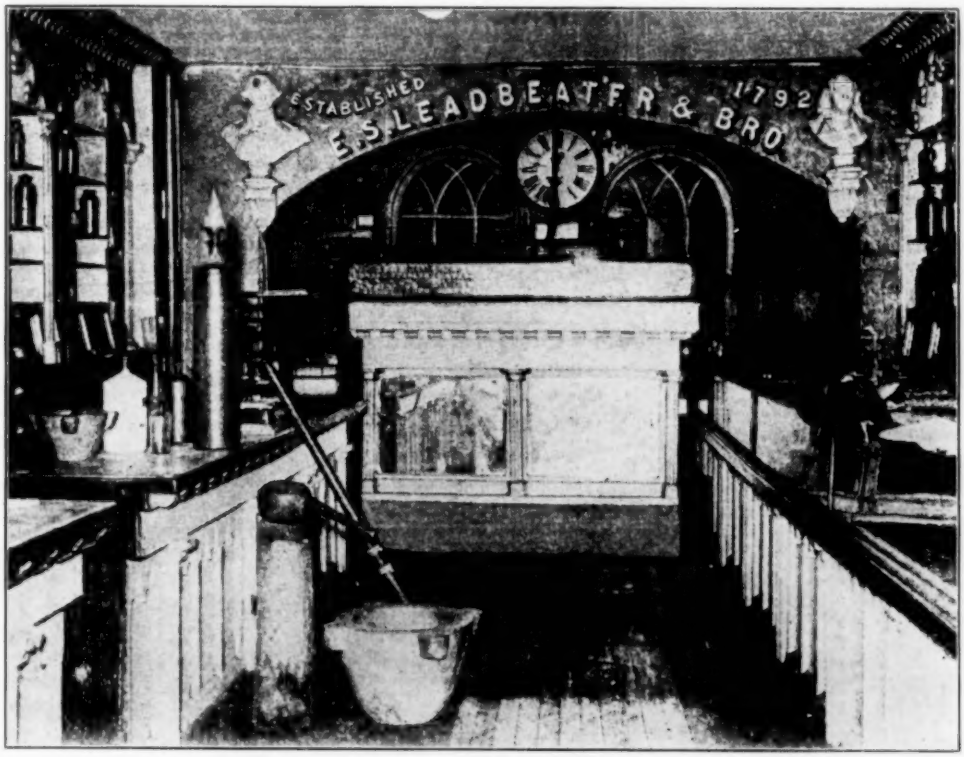
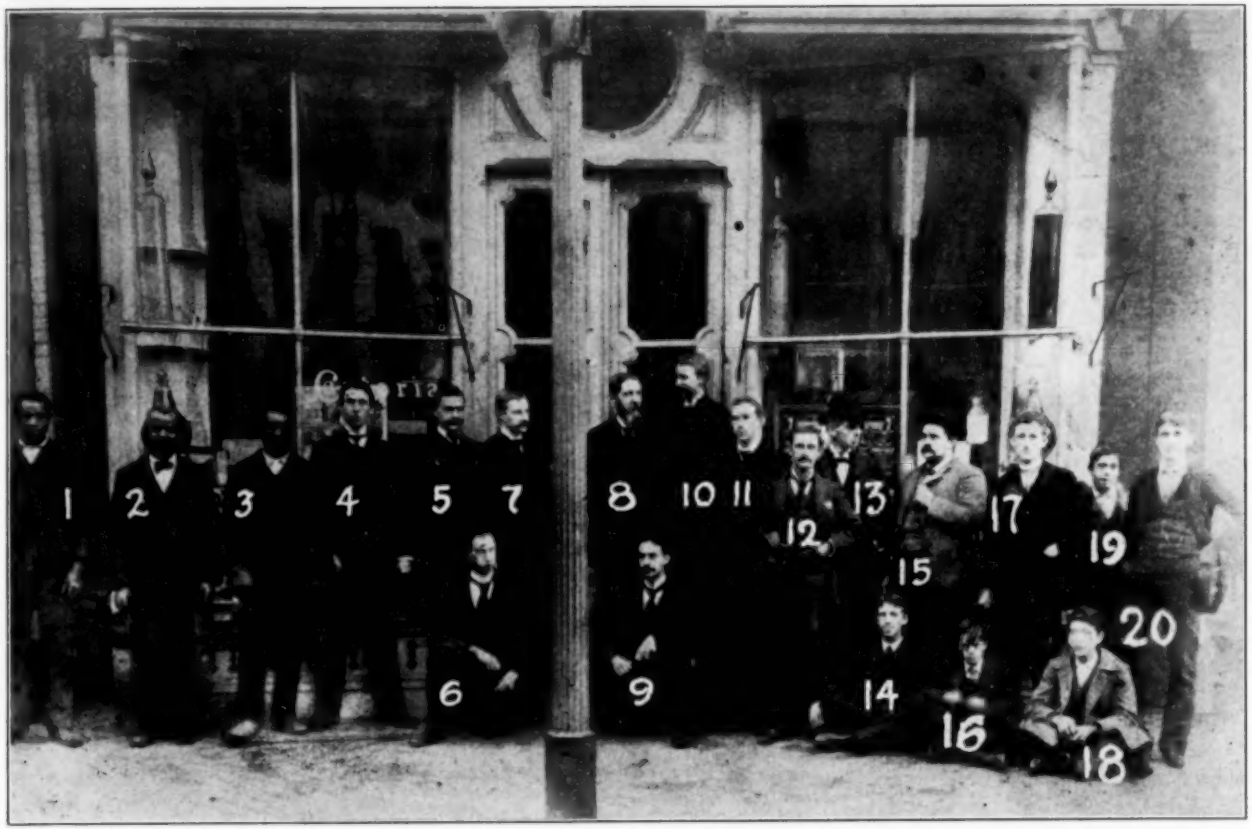


Leadbeater Pharmacy, interior. Founded by Edward Stabler, the fixtures, prescriptions, counters, blotters, etc., were purchased for the AMERICAN PHARMACEUTICAL ASSOCIATION.

Auction Sale of Leadbeater Pharmacy for AMERICAN PHARMACEUTICAL ASSOCIATION. The sale took place in a room next to the old pharmacy on July 19, 1933.



The print from which the cut herewith was made was presented by a member of the Washington family, a pharmacist residing in Logan, West Va. He and another pharmacist are in the group and a brother, also a registered pharmacist, are members of the family. More extended references appear on the title page.

JOURNAL OF THE AMERICAN PHARMACEUTICAL ASSOCIATION

VOL. XXVII FEBRUARY, 1938 No. 2

CONNECTING UP WITH PHARMACISTS OF AN EARLIER DAY.

When the group photograph shown on the title page was made, six of the members were known to be living, one indefinite and thirteen had ceased their labors. No. 7—Clarence Leadbeater, resides in Alexandria, Va.; No. 13—William Boothe, resides in Alexandria, Va.; No. 16—George Minnigerode, lives in Washington, D. C.; No. 17—William Griffith, lives in Alexandria, Va.; No. 18—J. A. Washington, resides in Logan, W. Va.; No. 19—Lawrence Washington, lives in Northfork, W. Va.

At the suggestion of Roy B. Cook, J. A. Washington donated the photograph to the AMERICAN INSTITUTE OF PHARMACY. He is a son of Lawrence Washington, and grandson of Col. John A. Washington—the last private owner of Mount Vernon; he and Lawrence Washington, Jr., are registered pharmacists in West Virginia; another brother—Preston C. Washington—is also a West Virginia Registered Pharmacist. It is interesting to record that three of the illustrious family are pharmacists.

On page 85 is shown the interior of the L. Leadbeater Pharmacy; this establishment succeeded the Stabler Pharmacy, founded by Edward Stabler in Alexandria. The stock and fixtures of the Pharmacy were purchased at auction for the AMERICAN PHARMACEUTICAL ASSOCIATION. Included, there is much historical matter—Prescription books, orders and invoices, shelf ware and utensils. It is hoped that an organization of Alexandria will create a fund for a museum, wherein this historical material may be placed on display. The sketch herewith will be supplemented in a later issue of the JOURNAL.

EDITORIAL

E. G. EBERLE, EDITOR 2215 Constitution Ave., WASHINGTON, D. C.

A NEW SPANISH EDITION OF THE U. S. PHARMACOPŒIA.

THE SPANISH Edition of the U. S. Pharmacopœia, Eleventh Decennial Revision (U. S. P. XI), sponsored by the Board of Trustees of the U. S. Pharmacopœial Convention, has just come from the press.

This edition was translated under the auspices of the Pan-American Sanitary Bureau in Washington. It forms a volume of 695 pages, with a detailed index, and at the end there is a list of official titles in both English and Spanish. Auxiliary Committees of Cuba, the Philippines and Puerto Rico took part in the work of translation.

This is the fourth edition of the U. S. Pharmacopœia which has been translated into Spanish and published by the U. S. P. Board of Trustees. It was originally provided for use in the Philippines and Puerto Rico and also in Cuba, where it was promptly adopted as the official Pharmacopœia. It is now also official in Costa Rica, Nicaragua (together with the French Codex), Panama and the Dominican Republic.

The Board of Trustees, in announcing this new edition to the health departments of the Republics of Central and South America, have expressed the hope that it may be useful to them in the preparation of their own Pharmacopœias, and that it may assist in bringing about uniformity in titles, strengths and standards of purity among the medicines used in Pan-American countries.

As it has required considerable time for the translation and printing of the Spanish Edition, alterations and corrections published in the U. S. P. XI First Supplement which became official December 1, 1937, have been incorporated.

The book is now on sale by the distributors, The Business Publishers International Corporation, 330 West 42nd Street, New York, N. Y., U. S. A.

MODERN POINTS OF VIEW AND METHODS IN PHARMACOGNOSY.

IN RESPONDING to the presentation of the Hanbury Medal at the London evening meeting of the Pharmaceutical Society Dr. Richard Wasicky responded with an address on the subject "Modern Points of View and Methods in Pharmacognosy." We share in the honor not only because of his distinction but also because he was elected *Honorary Member* at the New York meeting of the AMERICAN PHARMACEUTICAL ASSOCIATION. Liberty is taken in using an abstract of the address prepared by the *Chemist and Druggist* of February 12th:

"Pharmacognosy, as a pure science, aims at a scientific understanding of the drugs of vegetable or animal origin. Applied pharmacognosy uses the results of research for practical purposes in pharmacy, industry and in other spheres. Most of the older textbooks treat the morphology and histology of vegetable drugs in affectionate detail. In addition, they give brief particulars of the botanical and geographical sources of a drug, its mode of preparation, its components, its impurities and adulterations; a few animal drugs being discussed in an appendix. In the years succeeding publication of Hanbury & Flückiger's work pharmacognosy was

forced to devote more time to histology. Thus it was possible for the idea to become widely prevalent that pharmacognosy was more or less identical with the descriptive morphology and histology of vegetable drugs. But as these branches developed toward some sort of completion, wider interests again began to be cultivated. In London especially the spirit and influence of Hanbury continued to be effective."

DR. AUTUN URGOC-RICHARD WASICKY.
Hanbury Medalist.

"The address was presented as a résumé of the ideas and tendencies at work in the field of modern pharmacognosy and an outline of the principles that determine the attitude of the worker in pharmacognosy toward his science."

The speaker made reference to identification by taste and smell and stated that "it is astonishing with what reliability, at the Pharmaceutical Institute, University of Vienna, the students were able to determine the better value of various drugs, using brucine as a standard." In the modern methods, he said, "of cultivating medical drugs, attempts are made to enhance the effective power of drugs, but quantitatively and qualitatively. The measures employed are concerned partly with the growth of the plant up to the time when it is harvested, and partly with the processes by means of which all or part of the plant is converted into a drug."

Among the participants in the program of the evening were President Thomas Marns, of the Pharmaceutical Society and Dr. Adolf Kunz, representing the Austrian Minister, and Dr. and Mrs. Wasicky, a pharmacist and co-worker.

The *Pharmaceutical Journal* published the address in full and references to the publications are made. We are pleased to congratulate the recipient of the medal and British pharmacists.

HOSPITAL EXHIBIT AT THE NEW YORK WORLD'S FAIR.

THE *Journal of the American Hospital Association* reports on the hospital exhibit which is to be made at the New York World's Fair. The care of the patient in the hospital will be dramatically presented in a space of 1200 square feet. It will have as a purpose to make the laymen aware of the people who contribute to recovery in the hospital. Representatives of all departments and services will be shown. It states that 60% of the money of the hospitals comes from the patients and 30% from government and endowments.

The rural hospital is shown as a health center. An interesting graphic exhibit is included "that every four seconds a person enters a hospital, and the number of those who leave the hospitals cured."

The 10th International Congress of Military Medicine and Pharmacy will be held in Washington, D. C., May 7 to 10, 1939. Col. Harold W. Jones has been appointed secretary of the committee by President Roosevelt.

SCIENTIFIC SECTION

BOARD OF REVIEW OF PAPERS.—*Chairman*, F. E. Bibbins; H. M. Burlage, W. G. Crockett, E. V. Lynn, C. O. Lee, L. W. Rising, L. W. Rowe, Heber W. Youngken, Ralph E. Terry, Carl J. Klemme.

THE DOSE-RESPONSE RELATIONSHIP IN THE U. S. P. XI PARATHYROID ASSAY.*

BY LLOYD C. MILLER.

A monograph covering the assay of Parathyroid Extract was included for the first time in the 11th revision of the United States Pharmacopœia. In brief, the method calls for determination of the rise in serum calcium produced by a suitable dose of the material in normal male dogs of a specified weight. The question of what constitutes a suitable dose arose in applying the method in connection with the regulatory work on bioassay drug products under the Federal Food and Drugs Act. This paper records the results of our investigation on this phase of the method.

The method is based on the work of Collip and Clark (1), who published their results in 1925 on the responses of normal dogs to parathyroid hormone. They found that the proportion was fairly satisfactory between the amount of extract administered and the serum calcium rise. So far as the writer is aware, no confirmation of this work on normal dogs has been published. In 1935, Dyer (2) showed that with the rabbit as the test animal he was unable to obtain proportional rises in the serum calcium in response to graded doses of an active parathyroid preparation.

In view of the work of Collip and Clark (1) and of the wording of the pharmacopœial method, the inference seems clear that the following relationship should hold between dose and response:

$$\frac{\text{Mg.\% rise in serum calcium} \times 100}{\text{Cc. of extract}} = \text{U. S. P. XI units per cc. of extract.}$$

The factor 100 arises from the definition of the pharmacopœial unit. A unit represents one-hundredth of the amount of extract required to raise the calcium level of the blood serum of normal dogs by 1 mg. per 100 cc. of serum. No dosage has been suggested for the assay in the pharmacopœial monograph, but in practice most manufacturers stipulate that the dose they select in standardizing their extracts causes a rise in serum calcium between 4 and 6 mg.%. It has been the object of the present investigation to determine the responses to several parathyroid extracts when each was tested at various dosage levels. The results indicate that the selection of the dose is of considerable importance in arriving at the true potency of the test material.

EXPERIMENTAL.

The dogs were kept on a diet of commercial dog biscuit supplemented with cod liver oil to insure an adequate vitamin D intake. The calcium content of this diet was about 2.2%. The

* From the Division of Pharmacology, Food and Drug Administration, United States Department of Agriculture, Washington, D. C.

phosphorous content was approximately 1.2%, so that the Ca:P ratio was about 2:1. In compliance with the pharmacopœial requirements the dogs were all healthy, mature males weighing between 10 and 12 Kg. Each test covered a 24-hour period which began with the drawing of the initial blood samples between 9:00 and 10:00 A.M. The dogs were fed as usual about 1:00 P.M., and the test material was injected subcutaneously between 4:00 and 5:00 P.M. The next day the second blood samples were drawn between 9:00 and 10:00 o'clock, which was 16 to 17 hours after injection of the extract. All the test material was U. S. P. Parathyroid Extract prepared, presumably, under the Hanson patent by well-known commerical firms. The labeled concentration was 100 U. S. P. units per cc. Thus the serum calcium rise to be expected was 1 mg.% for each cc. of the extract injected. The serum calcium was determined in duplicate by the Clark-Collip procedure, which has been proposed for U. S. P. adoption (3). This method has given closely reproducible results, and the claim for its accuracy has been verified, since duplicates usually agree within ±1% of the mean value. Even though an error of ±1% in estimating 10 mg. of calcium in 100 cc. of serum seems small, it can give rise to an error of ±5% in the determination of an increase of 4 mg. per 100 cc. With smaller increases in serum calcium, the limits of possible error are proportionately greater, hence the desirability of aiming for increases of 4 to 6 mg.%. All the normal serum calcium levels of the dogs used in this study have been between 10 and 12 mg.%. This represents greater uniformity in the normal levels than has been reported in most parathyroid studies and perhaps is a reflection of the rigid requirements for the animals laid down by the Pharmacopœia.

RESULTS.

Table I presents the results obtained by varying the dosage of the same parathyroid extract, sample No. 5988. The apparent potency varies from 75 to 222 U. S. P. XI units per cc., depending on the dose used. This discrepancy arises from the fact that the serum calcium increase caused by 2 cc. of extract is about as great as that produced by 6 cc. Four other samples have been tested over the same dosage range with similar results.

TABLE I.—DOSE-RESPONSE RELATIONSHIP, PARATHYROID EXTRACT No. 5988.

Dog No.	Dose Cc.	Mg.% Serum Calcium Rise.	Average.	U. S. P. XI Units Per Cc. of Extract.
30	1.25	2.62		
28	1.25	1.62	1.94	155
31	1.25	1.58		
30	2.00	4.49		
33	2.00	4.04	4.44	222
30	2.00	4.79		
32	3.00	4.18		
31	3.00	3.98		145
33	3.00	5.50	4.35	
33	3.00	3.69		
25	4.00	3.48		
30	4.00	4.21		96
28	4.00	4.69	3.82	
25	4.00	2.91		
26	6.00	5.96		
32	6.00	4.79		
25	6.00	3.05	4.51	75
31	6.00	4.43		
28	6.00	4.30		

In Table II are data obtained with another extract. It will be seen that the relationship between smaller doses and their respective responses approaches the

theoretical straight-line proportionality. In spite of the great variations in the individual tests, the average responses to doses of 1 to 3 cc. of this extract are fairly proportional. However, the 3-cc. dosage level marks the point where the theoretical proportionality between dose and response begins to fail. It is true that 4 cc. of this extract elicits a response that is almost equivalent, in terms of U. S. P. XI units per cc. of extract, to the response obtained with the smaller doses. There is little question, however, that the average increase of 5.25 mg.% of serum calcium obtained with this dose represents the maximum rise obtainable with this extract, since the response to 6 cc. shows that an increment of 50% in dosage did not cause any greater serum calcium rise.

From Table II it appears further that the "suitable dose" must be confined to rather narrow limits. The upper limit is defined by the plateau above which the serum calcium cannot be raised. This is represented by increases of 5 to 6 mg.% above normal in the dogs of our colony. It is necessary, therefore, to select a dose that is known, by previous trial, to produce a submaximal response. Otherwise, a serious error can arise in that the indicated activity will be lower than the actual potency. The lower limit of the suitable dose is defined by the greater variation and possibility of error associated with smaller serum calcium increases, such as 1 to 2 mg.%. It is almost needless to point out that a larger number of dogs should be used in each assay if the results are to be based on smaller calcium increases, unless the error in the calcium determination and the animal variation can be reduced. Our experience indicates that the most reliable results are to be obtained when the dose employed produces an average serum calcium rise of 3 to 4 mg.%.

The possibility of extending the limits of this working-range by varying the maintenance diet has been tested experimentally. Four dogs maintained on dog biscuit were treated with a given lot of parathyroid extract in doses of 2 and 6 cc. on three occasions, each at least 1 week apart. These dogs then received raw beef heart exclusively for 10 days, and their responses were determined to doses of 2 and 4 cc. of the same extract. As may be seen from Table III there was practically no difference in the character of the responses of these dogs attributable to the change in diet. These results were confirmed on another group of four dogs, which first received another lot of extract while on a meat diet, and then again received the same extract after being shifted to dog biscuit. The average responses of these animals while on a meat diet were serum calcium rises of 4.22 and 5.64 mg.% to doses of 2 and 6 cc. of extract, respectively. The average responses while on a dog-biscuit diet were 3.84 and 5.52 mg.% to doses of 2 and 6 cc., respectively. There are two reports in the literature relating to the effect of diet on the response of dogs to the parathyroid hormone which offer some basis for controversy; these are, however, based on experimental work which is not strictly comparable. Allardyce (4) ascribed superiority to a diet of meat when he found that four normal dogs receiving the same amount of hormone at weekly intervals showed somewhat less variation in response when on a meat diet than when on a cereal diet. Regnier and Simonnet (5), working with parathyroidectomized dogs, concluded that changing alternately from a diet of meat to one of bread did not influence the responses of their dogs to daily administration of the hormone. Our results on normal dogs confirm the experience of the latter authors.

As indicated before, the dogs were fed at the usual daily feeding hour on the days of the tests; this was 3 to 4 hours prior to the injection of the test material. In view of the relatively slow action of the hormone, it was felt that alimentary absorption would be complete considerably before the peak of the response to the hormone was reached. Furthermore, there would be less question of a lack of calcium for mobilization during the height of the effect when the animals were fed as usual. It seemed advisable, however, to determine whether the time of feeding influenced the relationship between dose and response. In tests varying the time of feeding with respect to the time of injection of the extract, dogs fasted up to 28 hours prior to and during the effect of the injection gave results of the same character as those given in Table II. Thus the use of fasting dogs does not simplify the problem of choosing a dose which will produce a proportional and uniform response.

TABLE II.—DOSE-RESPONSE RELATIONSHIP, PARATHYROID EXTRACT NO. 6033.

Dog No.	Dose Cc.	Mg.% Serum Calcium Rise.		U. S. P. XI Units per Cc. of Extract.
			Average.	
25	1.0	1.25		
28	1.0	2.15		
32	1.0	1.53		
33	1.0	.50	1.69	169
34	1.0	1.89		
37	1.0	1.58		
38	1.0	2.90		
25	1.5	1.64		
30	1.5	2.88		
31	1.5	3.70		
33	1.5	3.30	3.02	202
35	1.5	3.08		
36	1.5	3.23		
38	1.5	3.30		
25	2.0	2.10		
28	2.0	3.32		
30	2.0	3.32		
30	2.0	3.02	3.42	171
33	2.0	2.70		
36	2.0	4.70		
37	2.0	5.18		
38	2.0	3.99		
28	3.0	4.55		
28	3.0	5.35	4.83	161
31	3.0	4.65		
25	4.0	3.95		
26	4.0	5.40	5.25	131
30	4.0	6.95		
31	4.0	4.72		
31	6.0	5.14		
32	6.0	4.88	5.13	86
33	6.0	5.36		

Table IV shows the responses, expressed in U. S. P. units per cc. of extract, of Dogs 25 and 28 to similar doses of the same extracts. The results obtained with

TABLE III.—DOSE-RESPONSE RELATIONSHIP AND VARIATION IN DIET, PARATHYROID EXTRACT NO. 6069.

Dog Biscuit.					Beef Heart.				
Date (1937).	Dog No.	Dose Cc.	Serum Calcium Rise, Mg.%.	U. S. P. XI Units per Cc. of Extract.	Date (1937).	Dog No.	Dose Cc.	Serum Calcium Rise, Mg.%.	U. S. P. XI Units per Cc. of Extract.
6–15	28	2	4.01	200	8–27	28	2	4.87	244
7–27	28	2	4.49	224	9–3	30	2	2.26	113
8–3	30	2	4.64	232	8–27	31	2	2.80	140
7–27	31	2	4.50	225	9–3	32	2	4.88	244
6–15	32	2	3.01	150					
8–3	32	2	3.41	172					
				200 (Av.)					185 (Av.)
8–3	28	6	5.05	84	9–3	28	4	5.08	127
6–15	30	6	6.30	105	8–27	30	4	3.91	98
7–27	30	6	4.70	78	9–3	31	4	4.72	118
6–15	31	6	5.92	99	8–27	32	4	5.00	125
8–3	31	6	5.72	95					
7–27	32	6	5.05	84					
				91 (Av.)					117 (Av.)

Dog 28 are entirely typical of those obtained with all the other dogs in the colony, except Dog 25. The latter appeared to be hyposensitive to parathyroid hormone. Wherever a comparison is possible, it will be seen that the result obtained on Dog 25 is lower than that obtained at the same dosage on Dog 28. The greatest rise in serum calcium obtained at any time with Dog 25 was less than 4 mg.%. In each of the eleven other dogs of the colony, occasionally serum calcium increases of 5 to 6 mg.% were obtained following administration of 4 to 6 cc. of extract. There was no apparent reason why this one dog was slightly more limited in its capacity to respond to the hormone. This may be looked upon as simply an example of biological variation for which some provision might well be made in the official monograph. Despite its somewhat lower sensitivity, this animal showed quite a uniform gradation in response. Following doses of 1, 1.5, 2 and 4 cc. of sample No. 6033, it responded with serum calcium rises of 1.25, 1.64, 2.10 and 3.95 mg.%, respectively. The figures for potency corresponding to these responses are 125, 109, 105 and 99 units per cc., which indicate agreement within the experimental error of the calcium determination.

TABLE IV.—RESPONSES OF DOGS 25 AND 28 TO FOUR PARATHYROID EXTRACTS, APPARENT U. S. P. POTENCY AT THREE DOSAGE LEVELS.

Extract No.	Dose of Extract.					
	2 Cc.		4 Cc.		6 Cc.	
	Dog 25.	Dog 28.	Dog 25.	Dog 28.	Dog 25.	Dog 28.
5976	125	200	81	119		
5988		170	87 73	117	51	72
6017		195	92	123	55 63	106
6033	105	166	99			

This table also gives some idea of the response to repeated doses of the same extract in the same dog. On two different occasions Dog 25 received a given dose of the same extract. The corresponding duplicate responses agree rather well with each other. Actually, however, this is simply another manifestation of the general observation that with doses of 2 to 6 cc. the rise in serum calcium is around 4 to 5 mg.%. Hence any remarks regarding the accuracy of the method will have to pertain to responses which are known to be submaximal.

The conclusion to be reached from these results is that the U. S. P. XI method for Parathyroid Extract is satisfactory for purposes of standardization and certainly is wholly suitable for indicating an absence of parathyroid activity. Certain precautions must be observed: (1) The dose selected must be shown to produce significant but submaximal increases in the serum calcium of the dogs used; (2) for satisfactory accuracy, more than the minimum of five dogs must be used unless precautions are taken to standardize the reactions of the animals. Such standardization might well be accomplished by adopting as a reference standard a stable powder prepared by methods already published (6) and distributed by the Board of Trustees of the U. S. Pharmacopœial Convention.

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CONSTITUENTS IN CASCARA SAGRADA EXTRACT.

3. The Lipids and Glycosides.*,[1]

BY MELVIN W. GREEN, C. G. KING AND GEORGE D. BEAL.[2]

The most characteristic compounds, from a pharmaceutical point of view, in cascara bark, senna, frangula, rhubarb and aloes are polyhydroxyanthraquinones. The quinones are present largely as glycosides and it has been generally thought that such glycosides were of major physiological importance. This view has led Beal and Tumminkatti (1), Daels (2) and others to make a thorough study of analytical methods for determining free and combined anthraquinones. Sipple, King and Beal (3) have recently isolated a rhamnoside of emodin from cascara bark, but the compound did not possess striking physiological activity. In fact there is little evidence that the anthraquinones account for the greater part of the purgative activity of the above types of drugs. The present investigation has been directed toward finding further information concerning the active principles in cascara bark, using as a guide a method of assay that was developed in a preliminary part of the study (4).

* The authors are indebted to the Parke, Davis and Company for a research grant and a supply of cascara bark.

[1] Contribution No. 346 from the Department of Chemistry, University of Pittsburgh.

[2] Assistant Director, Mellon Institute of Industrial Research.

EXPERIMENTAL—1. CHEMICAL STUDIES.

Lipids.—A petroleum-ether extract of 570 Gm. of cascara bark yielded 5.5 Gm. of lipids which were saponified and fractionated by the familiar lead soap method of Varrentrapp (5). The results of this separation may be seen in Table I. The apparent small amount of linoleic

TABLE I.—SEPARATION OF THE LIPIDS FROM 500 GM. OF CASCARA BARK.

	Gm.
Saturated fatty acids	2.57
Unsaturated fatty acids	1.93
Oleic acid	1.31
Linoleic acid	0.02
Linolenic acid	0.25
Sterols	0.133

Volatile acids, equivalent to 13.0 cc. of *N* NaOH.

acid was probably due to loss of material into the oleic and linolenic acid fractions. Otherwise the composition of the lipid fraction presented nothing unusual. Rhamnosterol (m. p. 131°) was isolated as the major constituent of the sterol fraction and was further identified by its acetyl derivative (m. p. 119°).

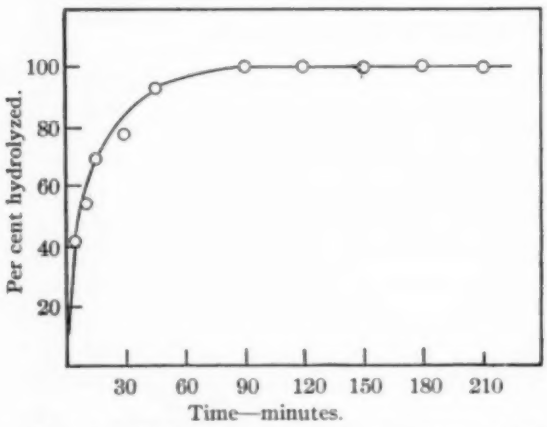

Fig. 1.—Hydrolysis of crude glycoside. Lead-complex from alcoholic extract of bark hydrolyzed at temperature of boiling water-bath in presence of HCl.

The marc from this petroleum-ether extraction was then exhausted with ethanol, from which a resinous precipitate gradually separated on standing. This resinous mass was subjected to steam distillation from which was collected about 5 liters of distillate. The distillate was shaken with large quantities of petroleum ether, yielding an essential oil and methyl hydrocotoin (2,4,6-trimethoxy benzophenone) (m. p. 115°). After the volatile oil had spontaneously evaporated, the methyl hydrocotoin was no longer readily soluble in petroleum ether, but was soluble in ethyl ether, acetone, chloroform and hot alcohol. The volatile oil was not identified.

Glycosides.—The alcohol-soluble extractives were hydrolyzed with hydrochloric acid and from the clarified hydrolysate rhamnose and dextrose were recovered. These sugars were identified chiefly by their osazones. The total quantity of sugars was determined by the Scales titration (6) and the dextrose was then fermented out with yeast. After fermentation, the sugars were again determined to provide an approximation of the rhamnose present. Only a very small quantity of rhamnose was fermented by the yeast under controlled conditions with known mixtures of glucose and rhamnose. By this means, the ratio of dextrose to rhamnose was found to be approximately 1:1. Supplementary fermentation tests with the organism B. rhamnosifermentans[1] also indicated that the second sugar was rhamnose, although we did not find such rapid gas production with rhamnose as one would expect from the results recorded by Castellani (7). Rotation values for the clarified sugar solutions also agreed with the values for glucose and rhamnose. The Seliwanoff test for ketoses was only faintly positive, and the mucic acid test was

[1] We wish to express our appreciation to Dr. A. Castellani for supplying a pure culture of B. rhamnosifermentans for fermentation tests. The qualitative differentiation of rhamnose from arabinose, xylose and the hexoses, on the basis of gas production by this organism, was in essential agreement with the results recorded previously.

negative, indicating that fructose and galactose were not present in significant quantities. The Kiliani test for desoxy sugars was also negative.

The rate of acid hydrolysis of a crude glycoside preparation was studied by determining the total sugars liberated at successive time intervals. The rapidity of hydrolysis (Fig. 1) indicated that the sugars were probably present in a true glycosidic linkage rather than in an ether linkage as suggested by Leger (8) for barbaloin from aloes. Complete hydrolysis occurred in less than 90 minutes, while in the case of barbaloin, Leger found that 8 hours were required to effect complete hydrolysis. Gardner and co-workers (9) obtained similar curves for the hydrolysis of synthetic glycosides of polyhydroxy-anthraquinones.

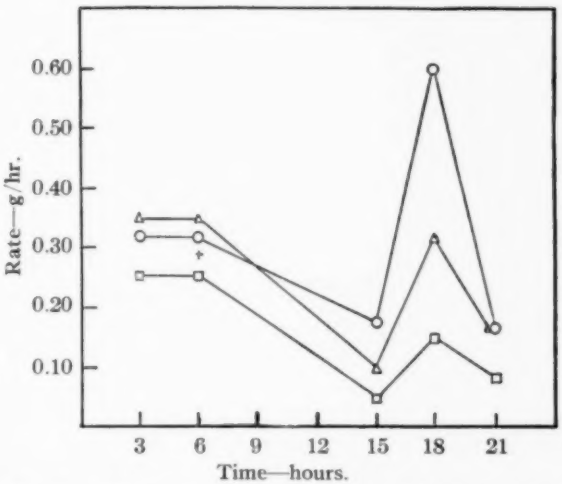

Fig. 2.—Effect of oxidation at elevated temperature on fluidextract of cascara.

○ Fluidextract (1.0 g.). □ Control.
△ Oxidized fluidextract (1.0 g.). + Cascara fed.

To obtain the aglycones, the hydrolytic residue was shaken with chloroform, the chloroform evaporated, and the residue taken up in toluene. By this means was obtained isoemodin, which was more soluble in toluene than emodin. Keimatsu and Hirano (10) have proved the formula of isoemodin by synthesis to be 3,5,8-trihydroxy-2-methyl-anthraquinone. Emodin is 1,6,8-trihydroxy-3-methyl-anthraquinone. The isoemodin was recrystallized several times from glacial acetic acid and acetylated with acetic anhydride in the presence of sodium acetate. The acetyl derivative was recrystallized from alcohol to a constant melting point. In addition, the hydranthrone was prepared by reduction of the anthraquinone with hydriodic acid. Table II gives the melting points and analytical data for these compounds.

TABLE II.—ANALYSIS OF CASCARA BARK CONSTITUENTS.

	M. P.* °C.	C %.	H %.	Ash %.
Isoemodin, calcd.	(212)	66.65	3.73	...
Found	212	66.41	3.97	...
Isoemodin acetate, calcd.	(New)	63.62	4.06	...
Found	184–185	63.40	3.86	...
Isoemodin hydranthrone, calcd.	(215–220)	74.19	4.71	...
Found	214–217	74.11	4.68	...
Methyl hydrocotoin, calcd.	(115)	70.56	5.92	...
Found	115	70.29	5.58	...
Solids from fluidextract		49.0	4.05	3.4
Solids from 48-hr. dialysate		50.3	5.3	4.2

* Values in parentheses represent published data.

2. PHYSIOLOGICAL STUDIES.

The authors have previously described a method of assay for cascara (4), using guinea pigs as test animals. The degree of catharsis was determined by the rate of fecal output (expressed in Gm. per hour), the feces being collected and weighed every three hours except during the over night period of 9 hours before catharsis

began. Control animals were given 1 or 2 cc. of water to eliminate differences due to the handling of the animals. Food cups were withdrawn during the assay period to keep the peristaltic stimulation of food at a minimum and to avoid appetite differences subsequent to dosage. The fluidextract of the U. S. P. XI was used as a standard cascara preparation against which the various fractions were measured. A single dosage was given after a six-hour period (generally 4 to 10 P.M.) had permitted matching the animals for comparable and normal groups.

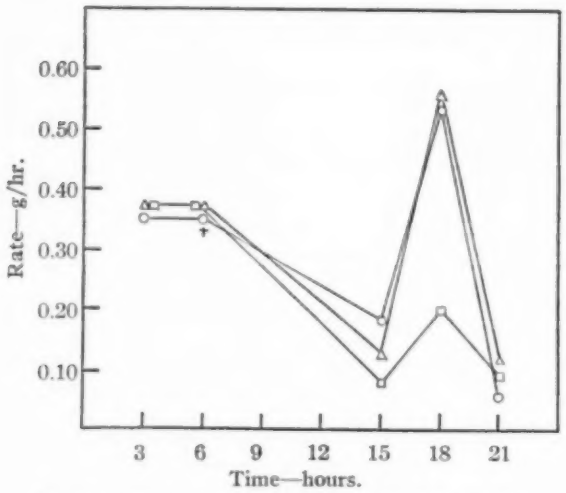

Fig. 3.—Effect of acid hydrolysis on fluidextract.
○ Fluidextract (1.0 g.). □ Control.
△ Hydrolysate (1.0 g.). + Cascara fed.

Oxidation of the fluidextract by bubbling air through it for three hours at the temperature of a boiling water-bath showed an approximate loss of 50% as shown in Fig. 2.

Since it had been thought that the purgative activity was due to the presence of the previously mentioned glycosides, a portion of the fluidextract was completely hydrolyzed at p_H 3.0 for two hours and the hydrolysate fed. Figure 3 indicates that the effect of hydrolysis was negligible. The positive control material (fluidextract) was held at the same temperature at a p_H of 6.8. Statistical analysis of the two curves based on the probable error of differences indicated that the differences were not significant.

Petroleum ether, alcohol and ethyl acetate were used as bark extractants and the corresponding fractions were assayed for cathartic value. None of these fractions were as active as the fluidextract in doses one to five times larger than the standard when based upon the quantity of bark extracted. Mixtures of two or more fractions, in their natural proportions, were more effective than single fractions, but a mixture of all fractions failed to account for more than 60–70% of the fluidextract activity.

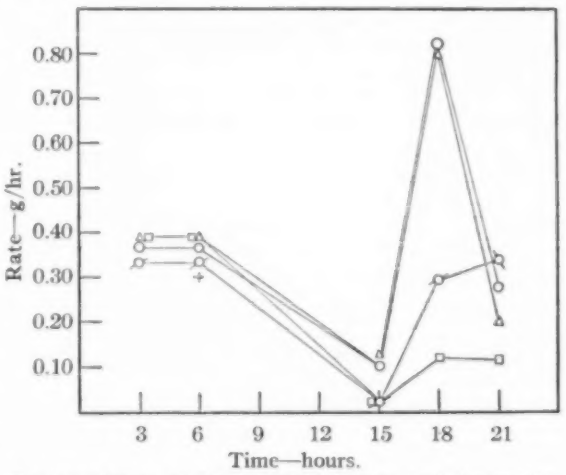

Fig. 4.—Assay of 48 hours dialysate and isoemodin.
○ Fluidextract (1.0 g.).
△ Dialysate (1.0 g.). ⌀ isoemodin (75 mg.).
□ Control.
+ Cascara fed.

Dialysis of the fluidextract (without alcohol) gave the most encouraging results for a means of separating active from inactive ingredients. The most active preparation was obtained from the material which dialyzed through a Visking artificial sausage skin membrane in 48 hours. This material was found to be at least equivalent in activity to the fluidextract when fed on the basis of total solids (Fig. 4). Under these conditions the dialysate fed was equivalent to 1.8 Gm. of bark, while the fluidextract was equivalent to 1.0 Gm. of bark. The material retained by the membrane exhibited some activity but it was very low compared to the dialysate. The rest of the activity was presumably lost during evaporation. It is also evident in Fig. 4 that 75 mg. of isoemodin, a quantity much above that in 1 Gm. of bark, exerted only a mild catharsis. Dialysis of glucose and citric acid through the membrane indicated that glucose came to an approximate equilibrium in about 20 hours and the citric acid reached a similar state in about 5 hours. Neither the fluidextract nor the dialysate contained appreciable quantities of nitrogen as determined by the micro procedure of Koch and McMeekin (11) on the solids from 1 Gm. of bark. Table II shows the carbon, hydrogen and ash content of the solids from the fluidextract and the 48-hour dialysate.

DISCUSSION.

The relatively low activity of the separate alcohol, petroleum ether and ethyl-acetate extractives cannot be adequately explained at the present time. Possibly all of the activity was not extracted by the respective solvents, but this is unlikely because the marc after exhaustion by these solvents yielded only a negligible quantity of water extractives. Again, a change may have taken place during the processing of the crude extracts. After the solvent had been completely removed by evaporation under reduced pressure below 60°, the residue often did not redissolve in the solvent originally used. An aqueous solution of these fractions always contained considerable suspended matter, and in the case of the ethyl acetate fraction, the material was practically insoluble in water. It may be that the physico-chemical nature of the partially purified material was changed so greatly that the active compounds were absorbed too quickly from the anterior portion of the intestine and thus did not reach the colon in sufficient concentration to exert a normal effect. The fact that the dialysate most nearly approximated the original material is an argument against the latter view, however.

From the results of feeding of the anthraquinones and the fluidextract minus the anthraquinones, it is evident that these compounds contribute to the cathartic value of cascara in either the free or the combined state, but they do not account for all or the greater part of the activity.

From the observed rate of dialysis it is probable that the active constituents of cascara are of relatively low molecular weight. Since dialysis offers a convenient way of removing the bulk of the resinous material without losing appreciable activity, we intend to study the dialysate in more detail.

SUMMARY.

Methyl hydrocotoin has been found as a new ingredient in cascara and the presence of isoemodin and rhamnosterol has been verified. Rhamnose and dextrose were found in the approximate ratio of 1:1. The rate of hydrolysis of these sugars

from their glycosides indicates that they are present in a true glycosidic linkage rather than in an ether linkage as reported for barbaloin. From the results of animal feedings, it was found that dialysis gave the most expedient way of separating inert material from the active ingredients in cascara fluidextract. The lipid fraction from cascara bark was practically inert. Isoemodin was only slightly active in a 75-mg. dosage. The ethyl acetate and alcohol extracts from bark were less active than the standard fluidextract, on either a total solids basis, or on a basis of bark extracted.

Bubbling air through the fluidextract for three hours at boiling water-bath temperature caused a loss in activity of approximately 50 per cent.

The activity of the fluidextract was not altered appreciably by (*a*) complete hydrolysis of the glycosides present or (*b*) extraction of the free anthraquinones.

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THE STANDARDIZATION OF ERGOT—A COMPARISON OF RESULTS OBTAINED BY THE COLORIMETRIC, THE COCK'S COMB AND THE BROOM AND CLARK METHODS OF ASSAY.*

BY ASA N. STEVENS.[1]

Van Urk (1) was among the first to report a color reaction between the ergot alkaloids and para-dimethyl-amino-benzaldehyde. Smith (2) later modified van Urk's procedure by directly mixing a one per cent tartaric acid solution of the alkaloids with concentrated sulfuric acid containing para-dimethyl-amino-benzaldehyde. Allport and Cocking (3) then modified Smith's reagent by altering the acid concentration and introducing ferric chloride as a catalyst. The Allport and Cocking reagent is now used by a majority of workers and has been adopted by the British Pharmacopœia, 1932, Addendum 1935 (4), in the estimation of the ergot alkaloids.

Smith (2) was perhaps the first to propose a quantitative colorimetric assay for the alkaloids in fluidextract of ergot. Other methods of the same general nature appear in the British Pharmacopœia, 1932 (5) and the Methods of Analysis of the Association of Official Agricultural Chemists, Fourth Edition, 1935. In each of these methods only those alkaloids which are sparingly soluble in water are deter-

* Scientific Section, A. PH. A., New York meeting, 1937.
[1] Control Laboratories, Eli Lilly and Company.

mined. All of them fail to take into account the alkaloids which are readily soluble in water.

The method of Hampshire and Page (6) differs from the methods mentioned above in that the total alkaloids also are determined: those alkaloids which are readily soluble in water being calculated by difference.

A modification of Smith's quantitative colorimetric assay for the fluidextract of ergot has already been reported by the author in a previous communication (7) along with a comparative study of the results obtained using this modified procedure, the U. S. P. X (Cock's Comb) and the Broom and Clark (8) methods of physiological standardization.

It is the object of this paper to compare the results obtained by the colorimetric, the Cock's Comb (U. S. P. XI) and Broom and Clark (8) methods of assay.

For some time the author has been supplementing the official assay of various lots of fluidextract of ergot with the colorimetric determination of total alkaloids. This was accomplished by the following method.

METHOD FOR TOTAL ALKALOIDS.

An aliquot portion of the sample to be tested is pipetted into a Watkins (9) extractor and diluted to about 50 cc. with distilled water. This aqueous suspension is then made faintly alkaline to litmus with three per cent ammonia. A small piece of litmus is placed in the aqueous suspension as an indicator. Ether is then added and the alkaline solution extracted for four hours on a water-bath using just enough heat to cause continuous evaporation.

At the end of this time the apparatus is dismantled and the total ether extract transferred to a separatory funnel. The ether is extracted with one per cent aqueous tartaric acid solution, using 10-, 10-, 10-, 5- and 5-cc. portions, respectively. Test for complete extraction by shaking with an additional 5 cc. of 1 per cent tartaric acid solution. Add to 2 cc. of this additional acid extract 4 cc. of the para-dimethyl-amino-benzaldehyde reagent. No blue color should develop.

The combined aqueous tartaric acid solutions are then gently heated on a water-bath, in order to remove the ether, and then diluted to 50 cc.

Two tubes containing 1 and 2 cc., respectively, of this solution are prepared. To the first 1 cc. of distilled water is added. Then to each tube 4 cc. of *M*/60 para-dimethyl-amino-benzaldehyde in 65 per cent sulfuric acid containing 0.01 per cent ferric chloride is added. The tubes are then thoroughly mixed and allowed to stand for one-half hour. A blue color develops.

The tubes are then compared in a colorimeter with standards containing known quantities of ergotoxine ethanesulfonate. From this data the quantities of the alkaloid in the sample tested can be calculated.

Typical results, obtained by this procedure, as compared with those obtained by the Cock's Comb (U. S. P. XI) and the Broom and Clark methods of assay are shown in Table I. An average of the results obtained on thirty-three samples is also indicated.

TABLE I.

Sample No.	Cock's Comb (U. S. P. XI) % Activity.	Broom and Clark % Activity.	Colorimetric (Total Alkaloids) % Activity.
A	100	80	149.7
B	130	100	132.4
C	100	90	170.8
D	100	80	152.8
E	100	100	80.0
F	50	30	38.4
G	125	90	128.0
Average—33 samples	77.5	67.6	105.9

NOTE: U. S. P. XI Standard, ergotoxine ethanesulfonate, has been used in all determinations reported in this paper.

It will be noted in Table I that the colorimetric results obtained for the total alkaloids in fluidextract of ergot are, on the average, higher than those obtained by either of the physiological methods of assay.

Table II gives the colorimetric results obtained, on samples of fluidextract of ergot, for those alkaloids which are sparingly soluble in water, and for the total alkaloids. Assay results obtained by the official Cock's Comb method are also tabulated for comparison.

TABLE II.

Sample No.	Cock's Comb (U. S. P. XI) % Activity.	Colorimetric. Total Alkaloids % Activity.	Colorimetric. Alkaloids Sparingly Soluble in Water % Activity.
1	95	126.8	99.6
2	80	126.7	82.5
3	112	102.7	79.9
4	100	144.0	86.4

The results in Table II are interesting in that they indicate that the Cock's Comb method of assay has evaluated only those alkaloids in the fluidextract of ergot which are sparingly soluble in water. This apparently explains the difference recorded in Table I between the colorimetric assay figures for total alkaloids and those obtained by the physiological assays.

DISCUSSION.

Since the discovery that there are alkaloids in ergot which are readily soluble in water, Barger (10) has pointed out that the only specific biological test for these substances lies in the use of the puerperal (human) uterus. Davis, Adair, Chen, Swanson (11) have already maintained "that the Broom and Clark method is not suitable for the evaluation of the new ergot principle." The data presented in this paper quite definitely indicates that the U. S. P. XI method of assay fails to determine these new alkaloids.

The investigations reported by Smelt (12); Swoop, Cartland and Hart (13); Swanson, Powell, Stevens and Stuart (14), and the author (7) have demonstrated that Smith's quantitative colorimetric assay method, and certain modifications thereof, are as accurate a measure of those sparingly water-soluble alkaloids in fluidextract of ergot as are the Cock's Comb and the Broom and Clark methods of assay.

Obviously the modified Smith (7) assay procedure determines only those alkaloids which are sparingly soluble in water.

It is possible, however, to determine the total alkaloids in fluidextract of ergot by the method described elsewhere in this paper.

Therefore it seems reasonable to assume that the alkaloids which are readily soluble in water may be estimated as the difference between the result obtained for total alkaloids and that obtained for the alkaloids sparingly soluble in water. These alkaloids could then be calculated either as ergotoxine ethanesulfonate or as the new ergot alkaloid.

SUMMARY.

Data have been presented showing the comparative results obtained upon assaying various samples of fluidextract of ergot by the (*a*) Cock's Comb (U. S. P. XI); (*b*) the Broom and Clark; (*c*) the modified Smith quantitative colorimetric and (*d*) the colorimetric method described in this paper.

These results quite definitely indicate that the U. S. P. XI method of assay determines only those alkaloids in fluidextract of ergot which are sparingly soluble in water.

A method for the determination of total alkaloids in fluidextract of ergot has been given in detail.

The author is indebted to C. E. Powell for the Broom and Clark and to C. C. Hargreaves for the Cock's Comb assay results appearing in this paper. He also wishes to express his appreciation to E. J. Hughes for his friendly criticism.

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A FURTHER STUDY OF THE ASSAY OF NITROGEN MONOXIDE.*[1]

BY FREDERICK K. BELL, C. JELLEFF CARR AND JOHN C. KRANTZ,[2] JR.

INTRODUCTION.

The tenth revision of the United States Pharmacopœia gave neither a purity rubric nor an assay for nitrogen monoxide. In a previous communication to this Journal two of the authors with Reindollar (1) set forth a method of assay for nitrogen monoxide which depended upon the preferential solubility of the gas in water chilled to 0° C. Commercial samples were assayed and a standard sample of gas was assayed repeatedly. The probable error of a single determination of this series was 0.23 per cent. The method was made official in the eleventh revision of the Pharmacopœia and during the last two years has been subjected to careful scrutiny in the hands of many different analysts.

It is the purpose of this paper to present certain minor modifications of the method and further to compare it with the other procedures extant for assay of this gas.

EXPERIMENTAL.

Several samples of nitrogen monoxide of known N_2O content mixed with N_2 were prepared for us by Dr. Wardell of the Ohio Chemical Co. These gas mixtures were not compressed sufficiently so that a liquid and gaseous phase obtained in the cylinder as is present in the commercially

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* Scientific Section, A. Ph. A., New York meeting, 1937.

[1] The expense of this investigation has been defrayed by a grant from the Board of Trustees of the United States Pharmacopœial Convention.

[2] Department of Pharmacology, School of Medicine, University of Maryland.

compressed gas. These specimens were analyzed by the method now official in the Pharmacopœia with the following modifications. (1) The volume of gas employed was 50 cc. instead of 100 cc. This facilitates complete solution and thus diminishes the laboriousness of the determination and also the time required. These were criticisms which have been made against the method. (2) Into the upper end of the nitrometer was fused a 5-cc. pipette graduated in tenths of a cubic centimeter in order to permit a more accurate reading of the residual gas. (3) The balance bulb of the gas pipette was kept filled completely during the vigorous agitation.

Employing these modifications on gas mixtures of known N_2O content the following results were obtained.

(*a*)	N_2O content 99.8 per cent	11 determinations mean = 99.8	σ = 0.05 per cent
(*b*)	N_2O content 96.3 per cent	10 determinations mean = 96.8	σ = 0.30 per cent
(*c*)	N_2O content 94.6 per cent	10 determinations mean = 94.6	σ = 0.31 per cent
(*d*)	N_2O content 90.8 per cent	11 determinations mean = 90.9	σ = 0.34 per cent

DISCUSSION OF RESULTS.

Despite the laboriousness of the method the foregoing assays indicate that reasonably accurate and concordant results can be obtained by this method. The absolute accuracy of the method and the concordance of results are optimum when the purity of the gas is very high. In our previously reported experiments with a sample of gas assaying approximately 98 per cent σ = 0.34 per cent and in this series omitting the very concordant results obtained in the pure sample of gas the average of σ is 0.32 per cent.

The authors are fully cognizant of some of the shortcomings of this method. Our assays are run on samples where the impurity present is constantly nitrogen. Mixtures of other gases as impurities with varying degrees of solubility in water at 0° C. will affect the assay results. Besides, if concordant results are to be obtained the utmost meticulosity must be exercised in all of the details of the experiment, especially with reference to the absence of dissolved gases in the water used for the solution of the nitrogen monoxide.

Commercially in addition to the pharmacopœial method two other methods are in general use. The first which is official in the British Pharmacopœia of 1932 depends upon the freezing of the gas by means of liquid air and measuring the volume of the impurities which remain in the gaseous state. We have not yet had experience with this method. The second method depends upon exploding a measured volume of nitrogen monoxide after admixture with a definite volume of hydrogen and measuring the residual nitrogen. The Ohio Chemical Co. sent the authors complete equipment of this method and in this laboratory it has been given careful study. Very concordant results were obtained on standard mixtures of N_2O and N_2. However, it was observed that reversing the order of introducing the two gases into the explosion chamber influenced the result. Differences as high as 0.3 per cent were obtained by reversing the order of mixing the two gases. For pharmacopœial purposes the chief objection that the authors see to the method as it is now employed is the high degree of purity required for the hydrogen and the fact that its absolute percentage strength must be ascertained before using it in the assay, especially since the principal impurity in commercial hydrogen is oxygen. It is readily seen that any oxygen present will combine with its equivalent of hydrogen under the experimental conditions prevailing in the explosion method. Thus, the presence of 0.1 per cent oxygen in the hydrogen employed will cause an error in the final assay

of the nitrogen monoxide of 0.3 per cent. Therefore, if this assay were made official, hydrogen would have to be recognized as a reagent and a method of determining its purity within 0.1 per cent would be necessary.

SUMMARY.

1. The water solubility method of assay of nitrogen monoxide has been further studied and with certain minor modifications it was found again to yield reasonably accurate and concordant results on standard mixtures of N_2O and N_2.

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DRUG EXTRACTION. XV. A STUDY OF FRACTIONAL PERCOLATION.*,[1]

BY WILLIAM J. HUSA[2] AND C. L. HUYCK.

In previous experiments by the present authors it was found that fractional percolation was successful for fluidextract of belladonna root and fairly successful for fluidextract of nux vomica (1).

Further research has been carried out to determine the efficiency of U. S. P. XI fractional percolation and N. F. II fractional percolation as compared with ordinary percolation. The relative efficiency of the different processes was determined by comparing the reserve percolates and finished fluidextracts as to content of alkaloids and extractive matter and by noting the time required in each case. In some instances analyses were also made of various fractions of weak percolate in order to throw further light on the progress of the extraction at various stages of fractional percolation.

HISTORICAL REVIEW.

In 1833, M. Boullay (2) of France suggested an extraction process for difficultly extractable substances, called "continuous displacement," in which the drug was divided in several containers and the liquid allowed to pass successively from one to another. E. R. Squibb (3) modified this process in 1866 by collecting a reserve percolate and several fractions of weak percolate from each portion of drug. At first Squibb called this method "divided percolation," but in 1867 he introduced the term "repercolation" (4). The name "fractional percolation" was applied by Diehl (5) to a repercolation process in which no weak percolate was left when the fluidextract was completed.

The greatest disadvantage of Squibb's repercolation process was that when a fluidextract was prepared some weak percolate remained which had to be kept in storage until the next time the fluidextract was made. After further experiments, notably by Squibb (6), Diehl (5), Lloyd (7) and Hallberg (8), a fractional percola-

* Scientific Section, A. PH. A., New York meeting, 1937.

[1] This paper is based on part of a dissertation presented to the Graduate Council of the University of Florida by C. L. Huyck, in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

[2] Head Professor of Pharmacy, University of Florida.

tion process was included in the first edition of the National Formulary in 1888. The N. F. process divided 16 troy ounces of drug into three portions of 8, 5 and 3 troy ounces, respectively, and no weak percolate was collected from the last portion. The later fractional percolation processes which have been official in the U. S. P. and N. F. have all been of the same type as that of the N. F. I, with only minor changes in details.

EXPERIMENTAL PART.

Materials Used.—To insure uniformity throughout the experimental work all of the drug used was from a thoroughly mixed 100-lb. portion of moderately coarsely powdered belladonna root. The menstruum used was a mixture of four volumes of alcohol and one volume of distilled water as specified for fluidextract of belladonna root in the U. S. P. XI.

Methods of Analysis.—Alkaloids were determined by the U. S. P. XI assay process for fluidextract of belladonna root. To determine total extractive, ten cc. of the liquid was evaporated to dryness on a water-bath and then heated in an oven at 105° C. until the difference between two successive weighings did not exceed ten mg.

Preparation of Fluidextract of Belladonna Root by Percolation.—Two separate 1000-cc. portions of fluidextract of belladonna root were made by ordinary percolation. In each case a 1000-Gm. portion of drug moistened with 600 cc. of menstruum was placed in a percolator in about five portions with agitation after each addition to promote even distribution, and after all the drug had been thus introduced it was packed down from the top, using a wooden potato masher and starting with light pressure which was gradually increased.

After macerating for forty-eight hours the percolate was allowed to flow at a rate of two cc. per minute, a reserve portion of 800 cc. and 2200 cc. of weak percolate being collected in each case. The weak percolate was placed in a vacuum distillation apparatus and evaporated at a temperature not exceeding 60° C. In the case of the fluidextract designated as "A," the vacuum distillation was continued until bubbles no longer were formed on the surface of the residue; with fluidextract "B" vacuum distillation was continued until no more distillate came through the condenser. As a result the residue in A was a soft extract which dissolved readily in the slightly warmed reserve portion while that from B was a much firmer extract which dissolved with difficulty. Fluidextract B showed much more precipitation than fluidextract A after storing one week.

Other experimental details were as follows: dimensions of percolators, length 56.5 cm.; internal diameter at the top, 11.3 cm.; length of drug column, 37 cm.; time of operator required for each portion of fluidextract, 4.2 hours; total elapsed time, 108.5 hours.

Analytical data on the finished fluidextracts are given in Table I.

TABLE I.—ASSAY RESULTS ON FLUIDEXTRACTS OF BELLADONNA ROOT MADE BY ORDINARY PERCOLATION.

	Gm. Alkaloids in 1000 Cc.	Gm. Total Extractive in 1000 Cc.
Fluidextract A	5.9	168.4
Fluidextract B	5.7	172.5
Average	5.8	170.4

Preparation of Fluidextract of Belladonna Root by U. S. P. XI Fractional Percolation.—Four different 1000-cc. portions of fluidextract of belladonna root were prepared by U. S. P. XI fractional percolation, using two different methods of packing. In the method of packing designated as "from top" the moistened drug was introduced into the percolator in small portions with slight agitation of the percolator to promote even distribution, and after all the drug had been thus introduced it was packed down from the top, using a wooden potato masher and starting with light pressure which was gradually increased. In the method of packing designated as "in sections," the drug was introduced in about eight portions and each separate portion packed down. The method of packing in sections gave tighter packing as evidenced by the smaller volume of packed drug. The proportion of menstruum used for moistening was 60 cc. per 100 Gm. of drug. The rate of percolation was 2 cc. per minute. The U. S. P. XI fractional percolation process was

followed with the exception that the final reserve portion of 500 cc. was collected in successive fractions of 300 cc. and 200 cc., respectively, in order to throw more light on the progress of extraction in the final stages.

Experimental details and analytical data are given in Table II. Of the four experiments, C and D were carried out simultaneously as a first series, and E and F made up a later series. The results of Experiments C and D indicated that the fluidextract prepared from the drug packed in sections contained slightly more alkaloids and extractive matter than the fluidextract prepared from the drug packed from the top. Packing from the top gave a larger volume of packed drug than packing in sections, but in the latter case the length of the drug column was greater because smaller percolators were used.

It seemed desirable to carry out another similar experiment in which the two different methods of packing would be compared using corresponding percolators of the same size. Accordingly, experiments E and F were carried out, using corresponding percolators of the same size for each method of packing. Under these conditions the greater drug volume obtained in packing from the top gave a longer drug column than was obtained by packing in sections.

The data in Table II indicate that the fluidextracts made by the two methods of packing in corresponding percolators of the same size were practically identical. Hence there seems to be no particular advantage in either method of packing in fractional percolation of belladonna root.

TABLE II.—PREPARATION OF FLUIDEXTRACT OF BELLADONNA ROOT BY U. S. P. XI FRACTIONAL PERCOLATION.

	Exp. C Packed from Top.	Exp. D Packed in Sections.	Exp. E Packed from Top.	Exp. F Packed in Sections.
Inside Dimensions of the Percolators in Gm.				
For 500-Gm. portion				
Length	42.5	36.5	42.0	43.0
Width (at top)	8.5	7.3	8.5	8.7
For 300-Gm. portion				
Length	36.5	29.5	37.0	36.3
Width (at top)	7.5	5.8	7.9	7.5
For 200-Gm. portion				
Length	28.5	27.5	29.0	29.0
Width (at top)	5.5	5.8	5.8	5.5
Volume of Packed Drug in Cc.				
500-Gm. portion	1325	1125	1300	1100
300-Gm. portion	750	675	750	650
200-Gm. portion	530	450	475	430
Total	2605	2250	2525	2180
Length of Drug Column in Gm.				
500-Gm. portion	26.0	27.0	27.5	25.0
300-Gm. portion	17.0	22.5	18.5	16.5
200-Gm. portion	21.0	17.5	19.0	18.5
Total	64.0	67.0	65.0	60.0
Average temperature during experiment	25° C.	25° C.	24° C.	24° C.
Time of operator required, in hours	2.2	2.9	2.1	2.7
Total elapsed time, in hours	176	176	176	176
Total Alkaloids in Various Fractions of Percolate, in Gm.				
First reserve—200 cc.	1.3	1.5	1.6	1.5
Second reserve—300 cc.	2.4	2.6	2.6	2.5
Third reserve				
First portion—300 cc.	1.5	1.3	1.6	1.8
Second portion—200 cc.	0.1	0.1	0.1	0.1
Total—1000 cc.	5.3	5.5	5.9	5.9

Total Extractive in Various Fractions of Percolate, in Gm.				
First reserve—200 cc.	20.1	19.8	19.0	20.2
Second reserve—300 cc.	39.3	40.1	37.4	37.4
Third reserve				
First portion—300 cc.	42.3	44.4	39.3	38.4
Second portion—200 cc.	18.9	20.4	21.3	19.4
Total—1000 cc.	120.6	124.7	117.0	115.4

Preparation of Fluidextract of Belladonna Root by N. F. II Fractional Percolation.—In the N. F. II fractional percolation method the drug and reserve percolate are divided into portions of 500, 325 and 175 Gm. and cc., respectively, as compared with 500, 300 and 200 Gm. or cc. in the U. S. P. XI process. Another difference is that the quantity of weak percolate collected from the second portion of drug is 650 cc. in the N. F. II as compared with 1000 cc. in the U. S. P. XI.

Fluidextract of belladonna root was prepared from two 1000-Gm. portions of drug, using the two different methods of packing previously described. The proportion of moistening liquid was 60 cc. per 100 Gm. of drug and the rate of flow was 2 cc. per minute.

The dimensions of the percolators used in Exp. G were the same as in Exp. C while those in Exp. H were the same as in Exp. D (see Table II). The temperature was approximately 25° C. The time of an operator required was 1.6 hours for Exp. G and 2 hours for Exp. H; the total elapsed time in each case was 176 hours. Further data are given in Table III.

TABLE III.—PREPARATION OF FLUIDEXTRACT OF BELLADONNA ROOT BY N. F. II FRACTIONAL PERCOLATION.

	Volume of Packed Drug in Cc.		Length of Drug Column in Cc.	
	Exp. G Packed from Top.	Exp. H Packed in Sections.	Exp. G Packed from Top.	Exp. H Packed in Sections.
500-Gm. portion	1300	1125	27.5	29.0
325-Gm. portion	875	750	22.0	27.5
175-Gm. portion	465	385	20.0	17.5
Total	2640	2260	69.5	74.0
	Gm. Alkaloids in Percolates.		Gm. Total Extractive in Percolates.	
First reserve—175 cc.	1.3	1.3	19.0	19.7
Second reserve—325 cc.	2.4	2.9	44.6	44.5
Third reserve				
First portion—300 cc.	1.5	1.3	43.7	42.0
Second portion—200 cc.	0.2	0.2	19.1	19.4
Total—1000 cc.	5.4	5.7	126.4	125.6

Within experimental error, the fluidextracts of belladonna root made by N. F. II fractional percolation contained the same proportion of alkaloids and extractive matter as were present in the fluidextracts made by U. S. P. XI fractional percolation. Apparently the differences in proportions of drug and reserve percolate in the two processes have no appreciable effect on the efficiency of extraction.

Analysis of the Repercolation Process.—In order to throw further light on the progress of extraction at various stages of fractional percolation, experiments were conducted in which analyses were made of the different fractions of reserve and weak percolate. Fractional percolation was conducted according to the U. S. P. XI directions, with the exception that the first portion of drug was doubled and the third portion reduced by one-half, in order that one-half of each fraction of weak percolate could be set aside for analysis. In addition to this, a 300-Gm. portion of drug was percolated with fresh menstruum, a reserve percolate of 300 cc. and five successive 200-cc. fractions of weak percolate being collected; by analyzing these percolates and comparing them with the percolates obtained from a 300-Gm. portion of drug percolated with weak percolate, it was possible to draw a conclusion as to whether weak percolate is a better solvent for the

active constituents than the original menstruum. Each percolation and each analysis was carried out in duplicate, the data in Tables IV–VI, inclusive, being averages.

Each portion of drug was moistened, allowed to macerate for fifteen minutes and packed from the top. The moistening liquid was used in the proportion of 25 cc. of liquid to 100 Gm. of drug. The rates of flow in fractional percolation were 3.5 cc. per minute for the 1000-Gm. portions of drug, 1.8 cc. per minute for the 300-Gm. portions and 1.3 cc. per minute for the 100-Gm. portions. For the 300-Gm. portion of drug percolated with fresh menstruum the rate of flow was 2.5 cc. per minute.

The finished fluidextracts made by fractional percolation (Exps. I and J) contained 5.7 Gm. of alkaloids and 149 Gm. of total extractive in 1000 cc. of fluidextract. The weights of alkaloids and total extractive in the various fractions of percolate were recalculated on a percentage basis, taking the quantities present in the finished fluidextracts as 100%. The figures thus obtained show the percentage of total extracted alkaloids and extractive present in each fraction of reserve and weak percolate; these data are presented in Table V.

The data in Tables IV and V indicate the rate at which the extraction of belladonna root proceeds at various stages of fractional percolation. The reserve percolates from the first two portions of drug contain a large proportion of the alkaloids present but complete exhaustion of the alkaloids in the drug proceeds slowly after that, since even the fifth portion of weak percolate contains about one or two per cent of the total alkaloids present in the three portions of drug taken as a whole.

TABLE IV.—ANALYSES OF ALL FRACTIONS OF PERCOLATE IN PREPARATION OF FLUIDEXTRACT OF BELLADONNA ROOT BY U. S. P. XI FRACTIONAL PERCOLATION.

From 1000-Gm. Portion of Drug.	Gm. Alkaloids in Fraction of Percolate.	Gm. Total Extractive in Fraction of Percolate.
Reserve—400 cc.	4.31	63.9
Weak percolate—600 cc.	0.81	73.4
Weak percolate—600 cc.	0.26	46.4
Weak percolate—600 cc.	0.20	21.1
Weak percolate—600 cc.	0.19	6.2
Weak percolate—600 cc.	0.23	3.5
Total	6.00	214.5
From 300-Gm. Portion of Drug.		
Reserve—300 cc.	1.92	51.8
Weak percolate—200 cc.	0.20	23.4
Weak percolate—200 cc.	0.14	17.6
Weak percolate—200 cc.	0.08	13.6
Weak percolate—200 cc.	0.07	10.2
Weak percolate—200 cc.	0.04	6.9
Total	2.45	123.5
From 100-Gm. Portion of Drug.		
Reserve—250 cc.	0.81	37.2

TABLE V.—PERCENTAGE OF TOTAL EXTRACTED ALKALOIDS AND EXTRACTIVE PRESENT IN VARIOUS FRACTIONS OF PERCOLATE.

First Portion—500 Gm.	Per Cent of Total Alkaloids.	Per Cent of Total Extractive.
Reserve—200 cc.	37.9	20.2
Weak percolate—300 cc.	7.1	23.2
Weak percolate—300 cc.	2.3	14.7
Weak percolate—300 cc.	1.8	6.7
Weak percolate—300 cc.	1.8	2.0
Weak percolate—300 cc.	2.0	1.1

Second Portion—300 Gm.		
Reserve—300 cc.	33.7	32.8
Weak percolate—200 cc.	3.5	14.8
Weak percolate—200 cc.	2.5	11.1
Weak percolate—200 cc.	1.4	8.6
Weak percolate—200 cc.	1.2	6.4
Weak percolate—200 cc.	0.7	4.4
Third Portion—200 Gm.		
Reserve—500 cc.	28.4	47.0

TABLE VI.—COMPARISON OF THE EXTRACTION OF 300-GM. PORTIONS OF BELLADONNA ROOT WITH FRESH MENSTRUUM AND WEAK PERCOLATE.

	Gm. Extracted Substances in Various Fractions of Percolate			
	Alkaloids.		Total Extractive.	
	Fresh* Menstruum.	Weak* Percolate.	Fresh* Menstruum.	Weak* Percolate.
Reserve—300 cc.	1.81	1.92	40.7	51.8
Weak percolate—200 cc.	0.10	0.20	15.4	23.4
Weak percolate—200 cc.	0.05	0.14	6.2	17.6
Weak percolate—200 cc.	0.03	0.08	2.3	13.6
Weak percolate—200 cc.	0.03	0.07	1.3	10.2
Weak percolate—200 cc.	0.03	0.04	1.0	6.9
Total	2.05	2.45	66.9	123.5

* Menstruum used.

According to Bennett and Cocking (9) a weak solution of the extractive of a drug is usually a better solvent for the active constituents than the original menstruum. From the data in Table VI and considering the quantity of alkaloids and extractive matter already present in the weak percolate from the first portion of drug (see Table IV) this statement does not appear to be true in the extraction of belladonna root. For this drug, at least, the only advantage in using weak percolate in fractional percolation is simply that a stronger percolate is obtained by using as menstruum a liquid which is already partly saturated with drug constituents.

DISCUSSION OF RESULTS.

Method of Packing.—In an earlier paper by the present authors (10) it was shown that packing the drug from the top was somewhat better than packing in sections in the percolation of belladonna root. In citing this paper, Büchi and Feinstein (11) stated that this was the first accurate study of efficiency of different methods of packing that was published in more than a century of percolation history. The conclusions reached by the present authors on belladonna root were verified in the case of cinchona by Büchi and Feinstein (11). Although there was a slight but definite difference in favor of packing from the top in simple percolation of both belladonna root and cinchona, the present investigation has shown that in repercolation of belladonna root the method of packing has no appreciable influence on the efficiency of extraction. In this connection it may be noted that the earlier study (10) showed that packing from the top was particularly advantageous in fast percolation conducted without maceration, the difference being much smaller when there was a forty-eight hour period of maceration after packing, as was the case in repercolation in the present study.

As may be seen in Table II, the volume of the packed drug was about ten per cent higher when packed from the top than when packed in sections. Büchi and Feinstein showed that lightly packed cinchona absorbed more menstruum than the

tightly packed drug. Likewise it was noted in the present study that more menstruum was used when the drug was packed from the top, this being due to the greater amount of menstruum remaining between the particles of the more lightly packed drug.

In making a 1000-cc. portion of fluidextract, the method of packing in sections required about 40 minutes longer than packing from the top.

Packing from the top is therefore advantageous in saving time of packing, and gives somewhat more efficient extraction in rapid percolation without maceration while packing in sections has the advantage of leaving less solvent to be recovered from the marc.

Comparison of Simple Percolation and Fractional Percolation.—The U. S. P. allows the use of Process C as an alternative for Processes A or B.

TABLE VII.—COMPARISON OF FLUIDEXTRACTS OF BELLADONNA ROOT MADE BY PROCESSES A AND C.

	Gm. Alkaloids in 1000 Cc.	Gm. Total Extractive in 1000 Cc.	Time of Operator Required in Hours.	Elapsed Time Required in Hours.
Process A (Percolation)	5.8	170.4	4.2	108½
Process C (Fractional percolation)	5.7	119.4	2.2	176

Comparative data on fluidextracts of belladonna root made by Processes A and C are given in Table VII. The fluidextract made by Process C contains about the same proportion of alkaloids as that made by Process A. Simple percolation, however, yields a fluidextract containing about forty per cent more total extractive than is obtained by fractional percolation. The greatly increased proportion of total extractive obtained by Process A is due to retention of much of the extractive matter present in the large proportion of weak percolate which is evaporated to a soft extract and dissolved in the reserve percolate. The difference in content of total extractive doubtless also causes a difference in alcohol contents of the fluidextracts; possibly this point has not received sufficient consideration in the past in setting official standards for alcohol content of fluidextracts.

Fractional percolation requires the packing of more percolators and the collection of more separate percolates than simple percolation but regardless of this it was found that Process A required almost twice as much of the operator's time as Process C, largely because of the time required in Process A for attention to the evaporation of the weak percolate *in vacuo* and the handling of the soft extract. On the other hand, the elapsed time required in fractional percolation was much greater, chiefly because of the time required for maceration and percolation of three portions of drug as compared with one portion in ordinary percolation.

Effect of Proportion of Moistening Liquid.—Husa and Yates (12) found that in simple percolation of belladonna root the efficiency of extraction was promoted by using a low proportion of menstruum in moistening the drug for preliminary maceration. In the present study, further data have been obtained in applying this principle to repercolation, the fluidextracts being prepared in 1000-cc. quantities.

TABLE VIII.—COMPARISON OF FLUIDEXTRACTS OF BELLADONNA ROOT MADE WITH DIFFERENT PROPORTIONS OF MOISTENING LIQUID.

	Gm. Alkaloids in Various Fractions of Percolate.		Gm. Total Extractive in Various Fractions of Percolate.	
	60 Cc.*	25 Cc.*	60 Cc.*	25 Cc.*
First reserve—200 cc.	1.6	2.2	19.0	31.9
Second reserve—300 cc.	2.6	1.9	37.4	51.7
Third reserve—500 cc.	1.7	1.6	60.6	74.2
Total—1000 cc.	5.9	5.7	117.0	157.8

* Quantity of menstruum used per 100 Gm. of drug for preliminary maceration.

From the data in Table VIII it is seen that the quantity of alkaloids in the first reserve is much greater when a smaller proportion of moistening liquid is used. In the second reserves the situation is reversed because the quantity of alkaloids which failed to reach the first reserve when more moistening liquid was used now is found in the second reserve. In the case of the alkaloids the advantage gained in the first reserve was lost by the time all three reserves had been collected. As to extractive matter, however, the use of a smaller proportion of moistening liquid gave more total extractive in each of the three reserves.

In securing efficient extraction of alkaloids, the use of only a small proportion of moistening liquid is not as advantageous as it is in simple percolation. However, the fact that a smaller proportion of moistening liquid gave a finished fluidextract containing considerably more total extractive than that made with more moistening liquid presents a problem that requires consideration. Whether the higher content of total extractive is desirable or undesirable is a debatable question. On the other hand it is clearly evident that fluidextracts made by different operators will vary considerably in alcohol content, specific gravity and content of total extractive unless the proportion of moistening liquid used is more rigidly standardized.

Proportion of Weak Percolate Collected in Fractional Percolation.—The various editions of the U. S. P. and N. F. have differed somewhat in the directions regarding the quantity of weak percolate to be collected from the second portion of drug in fractional percolation. At present both the U. S. P. XI and N. F. VI direct that 1000 cc. of weak percolate in five successive fractions of 200 cc. each shall be collected from the second portion of drug when making 1000 cc. of finished fluidextract. However, the U. S. P. VIII and IX required the collection of 800 cc. of weak percolate at this point, while the N. F. II and III required 650 cc.; in the N. F. IV and V the quantity was not definitely specified.

In seeking to specify a definite quantity of weak percolate there are obviously two opposing factors to be balanced. If the quantity of weak percolate from the second portion is too large, some of it will remain unused when the final reserve has been collected. If the quantity of weak percolate is too small at this point, it is necessary to use some fresh menstruum and the extractive value which this quantity of menstruum might have exerted on the second portion of drug is lost. Varying opinions as to how these two factors should be balanced doubtless account for the seeming vacillation in official standards on this point.

In the present study it was observed that when 1000 cc. of weak percolate is collected from the second portion of belladonna root, there is always a remainder of weak percolate when the third reserve has been collected; the portion remaining ranges from 150 to 250 cc. when making 1000 cc. of fluidextract. When 800 cc. of weak percolate is collected in accordance with the U. S. P. X directions, it was observed by the present authors in a previous investigation (13) that in making fluidextracts of belladonna root, nux vomica and cinchona there was a remainder of 40 to 55 cc. of weak percolate at the end of the process. In the present study it was found that when 650 cc. of weak percolate was collected from the second portion of belladonna root, as was directed by the N. F. II, more than 100 cc. of fresh menstruum was required to secure the full amount of reserve from the third portion of drug.

On the basis of our studies on belladonna root, nux vomica and cinchona, it is concluded that the collection of 800 cc. of weak percolate from the second portion of drug as specified in the U. S. P. X is satisfactory and that this proportion is preferable to that of the U. S. P. XI and N. F. VI, as well as to that of the N. F. II and III. The extra 200 cc. collected at present is of no value, since its content of dissolved substances does not appear in the finished fluidextract. On the other hand, the N. F. II and III did not make full use of the solvent power of all the menstruum used.

SUMMARY.

Fluidextract of belladonna root made by fractional percolation contains about the same proportion of alkaloids as that made by ordinary percolation but the latter contains a much higher proportion of total extractive matter. The preparation of a fluidextract by fractional percolation as compared with ordinary percolation requires less time of an operator but the total elapsed time is greater. Packing from the top is advantageous in saving time of packing, while packing in sections has the advantage of leaving less solvent to be recovered from the marc. Data are

presented showing the content of alkaloids and total extractive in every fraction of reserve and weak percolate collected in fractional percolation of belladonna root.

In experiments in which the proportion of moistening liquid was varied it was found that the use of a smaller proportion of moistening liquid gave a finished fluidextract containing considerably more total extractive. It is apparent that fluidextracts made by different operators will vary considerably unless the proportion of moistening liquid is more rigidly standardized.

On the basis of studies on belladonna root, nux vomica and cinchona, it is concluded that in fractional percolation the collection of 800 cc. of weak percolate from the second portion of drug as specified in the U. S. P. X is satisfactory and that this proportion is preferable to that of the U. S. P. XI and N. F. VI, as well as to that of the N. F. II and III.

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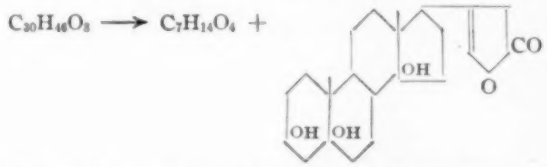
THE POTENCY OF PERIPLOCYMARIN, BUFOTALIN AND DESACETYL-OLEANDRIN.*

BY K. K. CHEN, ROBERT C. ANDERSON AND E. BROWN ROBBINS.[1]

Jacobs and Hoffmann (1) in 1928 isolated a cardiac monoside, periplocymarin, from the stems of *Periploca græca*, by his ingenious method of enzymatic digestion. Structural studies were carried out during subsequent years by Jacobs and Elderfield (2) and Elderfield and Rothen (3) until the following formula has been established (4):

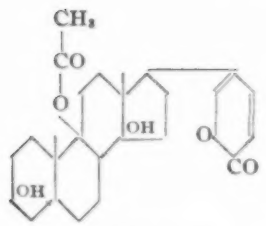


Periplocymarin Cymarose Periplogenin

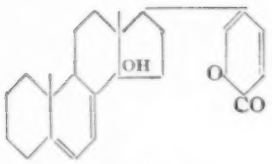
In 1913 Wieland and Weil (5) succeeded in crystallizing a cardiac principle, bufotalin, from the skin of the common European toad, *Bufo vulgaris* (*Bufo bufo bufo*), a substance resembling Abel's bufagin (6) but not identical with it. The constitution of bufotalin was repeatedly illucidated by Wieland (7), Wieland and Alles (8), Wieland, Hesse and Meyer (9), and Wieland and Hesse (10). A structural formula was finally proposed by Wieland, Hesse and Hüttel (11). As shown on page 114, it is

* Scientific Section, A. Ph. A., New York meeting, 1937.

[1] From the Lilly Research Laboratories, Indianapolis, Indiana.



Bufotalin



Scillaridin A

similar to that of scillaridin A (12). We attempted to isolate bufotalin from the secretion of *B. vulgaris*, but failed (13), while Wieland was always successful with one exception (14). It is not possible to account for the discrepancy at present.

Windaus and Westphal (15) in 1925 investigated the chemistry of oleandrin, a cardiac glycoside of the leaves of the plant *Nerium oleander*. Recently a similar product named folinerin has been studied by Flury and Neumann (16), and its potency has been determined in our laboratory (17). Additional chemical work carried out by Neumann (18) and Tschesche (19) shows conclusively that oleandrin is a derivative of gitoxigenin with an acetyl group on C_{16}, coupled with a molecule of oleandrose, and that oleandrin and folinerin are identical. The word folinerin can therefore be dropped from the scientific literature. The acetyl-free oleandrin which also occurs in nature is called desacetyl-oleandrin.

Although our chemical knowledge of the above substances has advanced, the exact potency of periplocymarin, bufotalin and desacetyl-oleandrin has never been determined. It is the purpose of this paper to report the data obtained with the three compounds. The bufotalin used in our experiments was courteously supplied by Professor Heinrich Wieland, München, Germany. Desacetyl-oleandrin was secured from Dr. Wilhelm Neumann, Würzburg, Germany, through the kindness of Dr. Rudolf Tschesche, Berlin. Periplocymarin was prepared from *Periploca græca*, crystallizing with one molecule of methyl alcohol, sintering at 138° C., and beginning to melt at 148° C. (corrected).

Our experimental procedures were the same as published previously (20). To effect a 0.1 per cent stock solution, periplocymarin was dissolved in 28.5 per cent ethyl alcohol (by volume), bufotalin in 47.5 per cent and desacetyl-oleandrin in 57 per cent. The results are shown in Tables I, II and III.

TABLE I.—AVERAGE FATAL DOSE OF PERIPLOCYMARIN, BUFOTALIN AND DESACETYL-OLEANDRIN IN CATS.

Drug.	Cat Number.	Sex.	Body Weight, Kg.	Fatal Dose, Mg. per Kg.	Average Fatal Dose ± Probable Error, Mg. per Kg.
Periplocymarin	1675	M	2.447	0.148	
	1676	F	2.116	0.139	
	1678	F	2.637	0.126	
	1679	F	2.196	0.174	
	1681	M	2.855	0.151	0.151 ± 0.004
	1682	M	2.417	0.160	
	1683	F	1.694	0.125	
	1684	F	2.158	0.145	
	1685	F	2.683	0.186	
	1686	F	2.182	0.157	

Bufotalin	1899	M	2.592	0.103	
	1900	M	2.547	0.116	
	1901	F	2.394	0.132	
	1902	M	2.264	0.134	
	1903	F	1.968	0.146	
	1904	F	2.760	0.101	0.130 ± 0.006
	1905	F	2.182	0.152	
	1906	M	2.151	0.160	
	1907	F	2.068	0.168	
	1908	F	1.720	0.083	
Desacetyl-oleandrin	1959	F	2.052	0.320	
	1960	F	2.227	0.258	
	1961	F	2.083	0.358	
	1962	F	2.334	0.230	
	1963	M	2.262	0.287	
	1964	F	1.949	0.409	0.308 ± 0.016
	1965	F	1.855	0.300	
	1966	F	2.242	0.252	
	1967	F	1.918	0.448	
	1968	F	1.854	0.219	

TABLE II.—MINIMAL SYSTOLIC DOSE OF PERIPLOCYMARIN, BUFOTALIN AND DESACETYL-OLEANDRIN IN FROGS.

Drug.	Concentration.	Dose, Mg. per Gm.	Number in Systole/ Number of Frogs Used.	Minimal Systolic Dose, Mg. per Gm.
Periplocymarin	1:20,000	0.00054	0/4	
		0.00064	0/4	
		0.00073	0/4	
		0.00909	0/4	
		0.00182	0/4	0.00318
	1:2,000	0.00273	3/8	
		0.00318	3/4	
		0.00364	7/8	
	1:1,000	0.00455	3/4	
		0.00909	4/4	
Bufotalin	1:500	0.00750	0/4	
		0.00833	2/8	0.00917
		0.00917	3/4	
Desacetyl-oleandrin	1:1,000	0.00208	0/2	
		0.00416	0/2	
		0.00667	0/2	
		0.00833	0/4	0.01167
		0.01000	0/4	
		0.01083	1/4	
		0.01167	3/4	
		0.01250	2/2	

It should be noted that in cats bufotalin proves to be less potent than areno-, quercico-, gama- and virido-bufagins, the results of which were recorded in a previous report (21); but it is decidedly more active than regularo-, vallicepo-, fowlero-, cino- and marino-bufagins. It is also more powerful than vulgaro-

bufotoxin, the conjugation product of bufotalin with suberyl-arginine isolated from the secretion of *Bufo vulgaris* (*Bufo bufo bufo*) (8), (13). The ratio of activity, between bufotalin and its bufotoxin is approximately 1:2.3.

TABLE III.—MINIMAL EMETIC DOSE AND PERSISTENCE OF ACTION OF PERIPLOCYMARIN, BUFOTALIN AND DESACETYL-OLEANDRIN IN CATS.

Drug.	Cat Number.	Sex.	Body Weight, Kg.	Initial Dose, Mg. per Kg.	Vomiting Occurred.	Final Fatal Dose, Mg. per Kg.	Interval between Initial and Final Fatal Doses, Hours.
Periplocymarin	1702	M	2.397	0.07	0	0.136	2.4
	1705	M	3.161	0.07	0	0.178	2.2
	1703	M	1.810	*0.08*	+	0.125	3.1
	1704	M	2.092	*0.08*	+	0.147	20.5
Bufotalin	1919	F	2.306	0.05	0	*	
	1920	F	1.755	0.05	+	0.173	1.9
	1921	F	2.333	0.05	0	*	
	1915	M	2.598	*0.06*	+	0.142	1.5
	1922	F	2.016	*0.06*	+	0.180	5.0
	1916	F	1.760	0.07	+	0.157	7.8
	1918	M	2.438	0.07	+	0.140	4.7
	1917	F	1.950	0.08	+	0.202	23.9
Desacetyl-oleandrin	1979	F	2.342	0.04	0	*	
	1976	M	2.157	0.05	0	*	
	1973	M	2.578	0.06	+	0.278	4.5
	1974	F	2.405	0.06	0	0.297	2.0
	1975	F	1.995	0.06	0	0.312	3.7
	1977	F	1.776	*0.07*	+	0.362	4.0
	1978	F	1.982	*0.07*	+	0.269	4.0
	1970	M	1.982	0.08	+	0.287	2.0
	1972	M	2.120	0.09	+	0.262	6.3
	1971	F	2.050	0.10	+	0.210	7.0

* Not determined.

Periplocymarin has practically the same cat unit (Table I) as scillaren A (20), regularo-bufagin (21) and coumingine hydrochloride (22). Its potency is lower than that of convallatoxin, β- and α-antiarins, ouabain, calotropin and cymarin, but it is more powerful than the remaining cardiac glycosides and alkaloids so far investigated in this laboratory.

In frogs (Table II), periplocymarin yields a larger minimal systolic dose than scillaren A and coumingine hydrochloride. Similarly bufotalin having the same cat unit as cymarin is 15.3 times less toxic than the latter to frogs. The disagreement of results by the cat method as compared with the frog method is a subject that will be discussed more fully at a later date.

The minimal emetic dose of periplocymarin (0.08 mg. per Kg.) in cats is equivalent to 53 per cent of the cat unit, and that of bufotalin (0.06) 46 per cent of its cat unit (Table III). Neither substance has a high persistence of action, for the final fatal doses of all the cats used for the emesis test are within the limits of the control series (see Table I).

Desacetyl-oleandrin, which is oleandrin minus the acetyl group, is definitely less potent than oleandrin (folinerin) either in cats or in frogs, particularly in the

latter (Tables I and II) (17). Neumann and Lindner (24) reported similar results. This is interesting, because in our previous work (23), (22) it was demonstrated that acetylation of cino-bufagin, marino-bufagin or cassaine reduced the cardiac activity in each case. Conversely, one would expect that the removal of the acetyl group increases the potency, but obviously with desacetyl-oleandrin this postulate breaks down. The minimal systolic dose of desacetyl-oleandrin in cats is 75 per cent larger than that of folinerin. In other words, the emetic action becomes greater when the acetyl group is intact. In the preceding article (22), it was shown that acetyl-cassaine is more emetic than cassaine, Gm. for Gm. With cino-bufagin, the acetyl derivative is equally effective in causing vomiting (23). Since acetyl-cino-bufagin has a larger molecule than the parent substance, the former is thus more emetic than the latter, molecule for molecule. On the other hand, acetyl-marino-bufagin is much less powerful in inducing emesis than marino-bufagin (22), just the reverse of the foregoing examples. This goes to show that it is difficult to predict the changes in physiological action following acetylation. It seems that different results may occur in the acetylation by nature as compared with that by laboratory methods. The deletion of acetyl group from oleandrin contributes another interesting feature; that is, oleandrin has a slow and persistent action (17), while desacetyl-oleandrin causes vomiting within 8 to 20 minutes (average 14 minutes), and also leaves the circulation more promptly. As shown in Table III, the final fatal doses with one exception (cat numbered 1971), determined 2 to 7 hours after the initial dose, all appear to lie within normal limits (compare Table I).

SUMMARY.

The potency of periplocymarin, bufotalin and desacetyl-oleandrin has been carefully determined.

Periplocymarin has approximately the same cat unit as scillaren A and coumingine hydrochloride. It is less potent than convallatoxin, β- and α-antiarins, ouabain, calotropin and cymarin.

Bufotalin is less powerful than areno-, quercico-, gama- and virido-bufagins, but more powerful than other bufagins so far investigated. It is 2.3 times more potent than vulgaro-bufotoxin, another cardiac principle occurring in the secretion of the same species of toads (*Bufo vulgaris* or *B. bufo bufo*).

Desacetyl-oleandrin is less active than the acetylated product oleandrin. Its effect appears to be more prompt and less persistent than that of oleandrin.

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The authors are indebted to Messrs. Chester C. Hargreaves and William T. Winchester for their valuable assistance in making the assays in frogs.

THE DETECTION OF CARBON MONOXIDE IN MEDICINAL OXYGEN.*[1]

BY FREDERICK K. BELL AND JOHN C. KRANTZ,[2] JR.

INTRODUCTION.

The eleventh revision of the United States Pharmacopœia includes a general test for the detection of carbon monoxide in the medicinal gases, oxygen and carbon dioxide. The procedure employed is a modification of the method set forth by Teague (1). In the Teague method thoroughly scrubbed, dried air is allowed to pass over heated, highly purified iodine pentoxide from which it quantitatively liberates iodine. The entire apparatus must be swept for hours and sometimes for days with carbon monoxide-free air in order to obtain a negative blank. To make this method applicable to medicinal oxygen we (2 and 3) inserted an additional I_2O_5 tube through which the gas to be tested was previously washed to remove any carbon monoxide that might be present. Thus the gas to be tested could be employed to scrub the iodine pentoxide that was to be used in the test.

Since this method became official it has become the subject of careful investigation on the part of manufacturers of medicinal gases. The principal criticism of the method is the difficulty and time involved in the obtaining of a negative blank and the complete failure to obtain a negative blank in the hands of certain experimentors. Success or failure in this endeavor depends first on the quality of the iodine pentoxide employed and secondly on the careful observance of all experimental details set forth in the method.

The experiments set forth in this communication describe a method for the detection of carbon monoxide in oxygen without the use of the troublesome iodine pentoxide.

EXPERIMENTAL.

The method developed depends upon the reduction of palladious chloride to palladium by the carbon monoxide (4). The flocculent metallic palladium in suspension reacts with a solution of ammonium molybdate producing molybdenum blue, the intensity of which is propor-

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* Scientific Section, A. Ph. A., New York meeting, 1937.

[1] The expense of this investigation has been defrayed by a grant from the Board of Trustees of the United States Pharmacopœial Convention.

[2] Department of Pharmacology, School of Medicine, University of Maryland.

tional to the absolute amount of carbon monoxide in the sample tested. For these tests a standard mixture of CO-O_2 was used. The carbon monoxide was prepared by the action of sulfuric acid on pure formic acid. The gas was liquefied and fractionated: the mixtures with oxygen were prepared for us by weight by Dr. Leo I. Dana of the Linde Air Products Company of Buffalo.

Procedure: Fill a 1000-cc. volumetric flask with distilled water and invert it over distilled water. Displace the water in the flask with the oxygen until less than 1 cc. of water remains in the inverted flask. Rapidly introduce 2 cc. of a saturated solution of palladious chloride, restopper and twirl the flask in order to bring the liquid and gas into intimate contact. The shaking is repeated intermittently for an hour and the mixture is then set aside for 12 hours in subdued light. Now add 2 cc. of ammonium molybdate solution (5 Gm. in 100 cc.), shake thoroughly and add 2 cc. of diluted hydrochloric acid. Allow the mixture to stand for one hour and then transfer to a suitable Nessler tube. Holding the tube over a white background and looking down through the liquid a bluish hue is observed in contradistinction to the yellowish green of a blank test.

DISCUSSION.

Using the foregoing procedure 10 p. p. m. of carbon monoxide in oxygen may be easily detected and in concentrations of 25 p. p. m. the deposit of metallic palladium prior to mixing with the ammonium molybdate solution is plainly visible. In applying this test many of the principal difficulties of the iodine pentoxide method are obviated. Nevertheless the non-specificity of the iodine pentoxide method obtains with the palladium procedure. Scrubbing with fuming concentrated sulfuric acid will easily remove one of the greatest offenders in this regard, namely, acetylene. As yet we have been unable to selectively absorb hydrogen, which if present in the oxygen tested in a concentration of 0.5 per cent gives a positive test.

Further experiments are being conducted to increase if possible the specificity of the test and to reduce the time required in which to perform it.

SUMMARY.

1. A procedure has been set forth for the purpose of detecting carbon monoxide in oxygen based upon the reduction of palladious chloride by the former. The sensitivity is of the order of magnitude of 10 p. p. m.

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A STUDY OF THE FACTORS INFLUENCING THE STABILITY OF LIQUOR MAGNESII CITRATIS, U. S. P. XI.*[1]

BY GEORGE E. CROSSEN AND CHAS. H. ROGERS.

Osol and Tice, in a recently published paper (20), report that stable samples of Solution of Magnesium Citrate can be prepared from 15 Gm. of an official magnesium carbonate and 33 Gm. of citric acid if the potassium or sodium bicarbonate is withheld until the product is dispensed. Such solutions, of course, contain nei-

* Scientific Section, A. PH. A., New York meeting, 1937.

[1] Abstracted from a thesis presented to the Graduate Faculty of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Science.

ther carbon dioxide nor alkali citrate during their time of storage. In addition, the quantity of citric acid necessary for the formation of these substances is still present in the solutions and available for combination with the magnesium. From the fact that precipitation did not occur in these unfinished solutions, it might be inferred that the stability of the finished official solution is influenced by the presence of the carbon dioxide or the alkali citrate, or by the lesser concentration of acid that results when these substances are formed. A number of variations of Solution of Magnesium Citrate were prepared for the purpose of determining the effect of these and other factors upon the stability of the official solution.

Six series of solutions were prepared, each series consisting of 20 solutions. Each solution within a series was made to contain a concentration of magnesium salt or salts differing from that of any other solution in the same series. Solutions bearing the same number and appearing in different series were made to contain the same equivalent quantity of magnesium oxide. The magnesium oxide used in the preparation of the solutions was analyzed and a quantity used which was calculated to make the solutions contain the MgO equivalents indicated in Table I.

TABLE I.—MgO EQUIVALENTS USED IN THE PREPARATION OF SOLUTIONS.

Solution Number.	MgO Used in 350 Cc. of Solution, Grams.	MgO Equivalent in Each 100 Cc. of Solution, Grams.
1	5.6000	1.6000
2	5.6735	1.6210
3	5.7820	1.6520
4	5.9045	1.6870
5	5.9430	1.6980
6	5.9745	1.7090
7	6.0305	1.7230
8	6.0550	1.7300
9	6.0655	1.7330
10	6.0865	1.7390
11	6.0914	1.7404
12	6.1085	1.7453
13	6.1338	1.7525
14	6.1530	1.7580
15	6.2055	1.7730
16	6.2580	1.7880
17	6.3175	1.8050
18	6.4190	1.8340
19	6.5415	1.8690
20	6.6500	1.9000

The weight of citric acid used in the preparation of those solutions that were not to be carbonated by the addition of a bicarbonate was calculated by subtracting the amount of acid necessary to form the normal alkali citrate by reaction with the bicarbonate (1.75 Gm.) from the quantity of acid which U. S. P. XI directs for the preparation of each bottle of the solution (33 Gm.).

Each solution was prepared by adding an accurately weighed quantity of magnesium oxide to a solution containing the required amount of citric acid, making the solution up to volume, heating, filtering, etc., as directed in the U. S. P. To prevent the growth of molds, a small crystal of thymol was added to each solution that was not to be carbonated.

The solutions in series A were prepared by dissolving the required amount of magnesium oxide in 100 cc. of a solution containing 312.5 Gm. of citric acid per liter. This solution was then made up to 350 cc. with distilled water and treated as described above.

It was calculated that 2.5 Gm. of potassium bicarbonate would form 2.55 Gm. of normal potassium citrate. Therefore, this amount of anhydrous salt was added to each of the solutions in Series B. In all other respects, these solutions were the same as those in Series A.

The solutions in Series C were prepared by dissolving the magnesium oxide in 100 cc. of a solution containing 330 Gm. of citric acid per liter, making the solution up to volume with distilled water, and adding 2.5 Gm. of potassium bicarbonate to the cooled solution immediately before the bottle was stoppered.

Series D, E and F were prepared in the same manner as were series A, B and C, respectively, with the exception that 60 cc. of official syrup were added to each solution before it was made up to volume.

The quantities of dibasic and tribasic magnesium citrates that would be formed by the complete reaction of each amount of magnesium oxide used with 31.25 Gm. of official citric acid and which, therefore, should be contained in the solutions prepared, were then calculated. The results of these calculations are given in Table II.

TABLE II.—CALCULATED QUANTITIES OF MAGNESIUM CITRATES CONTAINED IN SOLUTIONS PREPARED.

Solution Number.	Gm. of Salt in Each 100 Cc. of Solution.	
	$MgHC_6H_5O_7.5H_2O$.	$Mg_3(C_6H_5O_7)_2.14H_2O$.
1	12.0800	....
2	12.2500	....
3	12.5000	....
4	12.7500	....
5	12.8500	....
6	12.9100	....
7	12.7500	0.2000
8	12.6900	0.3011
9	12.6500	0.3360
10	12.6000	0.3930
11	12.5350	0.4670
12	12.4365	0.5535
13	12.3500	0.6970
14	12.2250	0.8295
15	12.0500	1.0310
16	11.8140	1.5000
17	11.5500	1.6690
18	11.0750	2.1320
19	10.6000	2.7160
20	10.0000	3.2850

After the solutions had been prepared, they were set aside and allowed to age. During this period of aging, they were inspected regularly and the appearance of a precipitate was noted. All of the solutions remained clear for three days after their preparation. After the expiration of this time, however, several of the more concentrated samples began to show definite signs of precipitation. This was first noted in solution F 20, and then spread rapidly to the more concentrated solutions in Series D and E as well as to other members of Series F. It was not until after two weeks of standing that precipitation was noted in any of the solutions that did not contain syrup, and then only in the most concentrated of these, solution C 20. The following table (Table III) shows the results of a survey of the solutions six weeks after their preparation. In this table, those samples in which a precipitate was found are marked +, whereas those in which no precipitation had occurred are marked −.

TABLE III.—RESULTS OF EXAMINATION OF SIX-WEEK-OLD SOLUTIONS.

Solution Number.	MgO in 100 Cc., Grams.	Series.					
		A.*	B.**	C.′	D.″	E.†	F.††
1	1.6000	−	−	−	−	−	−
2	1.6210	−	−	−	−	−	−
3	1.6520	−	−	−	−	−	−
4	1.6870	−	−	−	−	−	−
5	1.6980	−	−	−	−	−	−
6	1.7090	−	−	−	−	−	−
7	1.7230	−	−	−	−	−	+
8	1.7300	−	−	−	−	−	+
9	1.7330	−	−	−	−	−	+
10	1.7390	−	−	−	−	−	+
11	1.7404	−	−	−	−	−	+
12	1.7453	−	−	−	+	+	+
13	1.7525	−	−	−	+	+	+
14	1.7580	−	−	−	+	+	+
15	1.7730	−	−	−	+	+	+
16	1.7880	−	−	+	+	+	+
17	1.8050	−	−	+	+	+	+
18	1.8340	−	−	+	+	+	+
19	1.8690	−	−	+	+	+	+
20	1.9000	−	−	+	+	+	+

* Plain aqueous solutions of the citrates of magnesium.
** Aqueous solutions with potassium citrate.
′ Carbonated aqueous solutions with potassium citrate.
″ Solutions to which syrup had been added.
† Solutions with syrup and potassium citrate.
†† Carbonated solutions with syrup and potassium citrate.

In Table III, the influence of the sucrose contained in the syrup is shown in Series D and E. In both of these series, the more concentrated solutions precipitated; whereas the solutions in Series A and B, to which no syrup had been added, remained clear even after six weeks of storage. The effect of carbonation is shown in Series C, in which the more concentrated solutions precipitated whereas the solutions in Series A and B did not; and in Series F, in which more solutions contained precipitates than in either Series D or E. As a result of these observations, it can be stated that sucrose and carbon dioxide each contributed to the instability of the solutions studied.

The table also shows that the presence of an alkali citrate had no appreciable effect upon the stability of the solutions, since neither series B nor E showed any more precipitation than Series A or D, respectively.

The most important observation, however, is that none of the less concentrated solutions precipitated, regardless of the influence of the factors already mentioned. This indicates that the factor primarily responsible for the precipitation is the concentration of magnesium contained in the solution. Since the solutions in Series F resemble the official Solution of Magnesium Citrate very closely, the stability of the official solution can be predicted by a consideration of the behavior of the solutions in this series.

Comparison of the results obtained by the study of the solutions in Series F (Table III), with the calculated quantities of magnesium citrates in the solutions prepared (Table II), shows that all of those solutions that were calculated to contain tribasic magnesium citrate deposited a precipitate under the conditions encountered in the official solution. On the other hand, no precipitation occurred in those solutions calculated to contain only dibasic magnesium citrate. These calculations were based upon the complete reaction of the citric acid with the amounts of magnesium oxide listed in Table I. From this it becomes apparent that those official solutions prepared from 33 Gm. of citric acid and a quantity of magnesium oxide varying from 5.6 Gm. to 6.0 Gm. would be stable after the bicarbonate had been added, and would be within the official concentration range for Solution of Magnesium Citrate.

U. S. P. XI directs that the solution be prepared from 15 Gm. of magnesium carbonate, which is defined as "equivalent to not less than 39.2 per cent and not more than 41.5 per cent of MgO" (23). An accurately weighed 15-Gm. portion of this substance, therefore, is the equivalent of from 5.880 Gm. to 6.225 Gm. of MgO. The data given in Table III shows, however, that solutions containing the equivalent of more than 6.0 Gm. of magnesium oxide are unstable. In order to produce a stable solution by the use of 15 Gm. of an official magnesium carbonate, therefore, a sample which is equivalent to between 39.2% and 40.0% of MgO must be used. Obviously, it is not always possible to obtain magnesium carbonate having a magnesium oxide equivalent within this rather limited range. However, a stable solution can be prepared from any sample of magnesium carbonate of known MgO equivalent by using that quantity of the sample calculated to make each 350 cc. of the finished solution contain the equivalent of from 5.6 Gm. to 6.0 Gm. of MgO.

The calculated quantities of various magnesium carbonates equivalent to 5.8 Gm. of magnesium oxide are given in Table IV. Use of the weight of magnesium carbonate indicated opposite the MgO equivalent of the sample will yield a solution which conforms to the U. S. P. XI requirement with regard to magnesium concentration, and which is stable and can be stored without fear of precipitation.

TABLE IV.—QUANTITIES OF VARIOUS MAGNESIUM CARBONATES TO BE USED IN THE PREPARATION OF 350 CC. OF LIQUOR MAGNESII CITRATIS.

MgO Equivalent of Carbonate, Per Cent.	Wt. of Carb. to Be Used, Gm.	MgO Equivalent of Carbonate, Per Cent.	Wt. of Carb. to Be Used, Gm.
37.0	15.67	40.6	14.28
0.2	15.59	0.8	14.21
0.4	15.50	41.0	14.15
0.6	15.42	0.2	14.08
0.8	15.34	0.4	14.00
38.0	15.26	0.6	13.95
0.2	15.18	0.8	13.87
0.4	15.10	42.0	13.81
0.6	15.02	0.2	13.74
0.8	14.95	0.4	13.68
39.0	14.87	0.6	13.61
0.2	14.80	0.8	13.55
0.4	14.72	43.0	13.49
0.6	14.64	0.2	13.43
0.8	14.57	0.4	13.36
40.0	14.50	0.6	13.30
0.2	14.43	0.8	13.24
0.4	14.36	44.0	13.18

SUMMARY AND CONCLUSIONS.

(1) The influence of syrup; of potassium citrate; of carbon dioxide; of varying magnesium concentration; of a lesser concentration of citric acid; and of

combinations of two or more of these factors upon the stability of solutions of the citrates of magnesium was studied.

(2) The stability of these solutions was dependent upon the quantity of magnesium oxide used in their preparation, and was influenced by the presence of sucrose and carbon dioxide.

(3) Stable samples of Solution of Magnesium Citrate can be prepared according to the official formula if the magnesium carbonate used is the equivalent of from 39.2% to 40.0% of MgO. Since it is impractical, if not impossible, to obtain magnesium carbonate having an MgO equivalent within this range, the use of calculated quantities of magnesium carbonates having other equivalents is suggested and a table is given by means of which the necessary quantities of these carbonates can be ascertained

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PROFESSOR KARRER, NOBEL PRIZE WINNER.

The Nobel prize for chemistry has been divided between Prof. Dr. Paul Karrer of Zurich and Prof. W. N. Haworth of Birmingham, England. Professor Karrer, a native Swiss, is 48 years old. He served a year as assistant to Professor Werner at Zurich and then for six years was associated with Paul Ehrlich. In the spring of 1918 he was called to Zurich University as special professor and in the following year he was appointed ordinarius in the entire field of chemistry. In 1923 Karrer received the Marcel Benoist prize, a Swiss award, for his research on carbohydrates. In recent years Karrer's investigations of vegetable coloring matter and the vitamins have gained him an international reputation. The Nobel prize was awarded him in recognition of his research on the carotenoids, the flavins and vitamins A and G. A few years ago he also received the degree of doctor honoris causa from the medical faculty of Breslau University.

Professor Haworth received the prize in recognition of his research on carbohydrate and vitamin C.—*J. A. M. A.* (January 1, 1938).

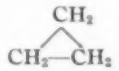
HOMOLOGUES OF CYCLOPROPANE—METHYL CYCLOPROPANE.*,[1]

BY W. A. LOTT, W. G. CHRISTIANSEN AND L. F. SHACKELL.

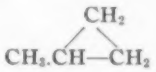
I. PREPARATION OF METHYL CYCLOPROPANE.*

BY W. A. LOTT AND W. G. CHRISTIANSEN.

When it was becoming apparent that despite its somewhat narrow margin of safety, cyclopropane was clinically useful so long as its administration was left in the hands of those familiar with its latent dangers, and when the advisability of supplying it generally was under cautious consideration, it occurred to us that we ought to determine whether homologues of it have any advantages over it for anesthetic purposes. Consideration was given first to the methyl cyclopropanes, the mono- and dimethyl compounds, and experimental work was directed first to the monomethyl cyclopropane which obviously is the one most closely related to cyclopropane. A quantity of it was produced and studied.



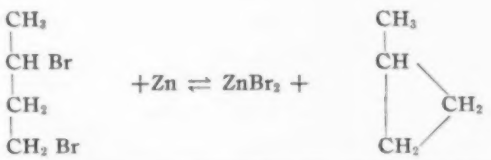
Cyclopropane



Methyl Cyclopropane

It was recognized that if methyl cyclopropane should prove superior to cyclopropane it would have certain additional advantages over cyclopropane due to the fact that its boiling point is 4–5° C. as compared with −34° C. in the case of cyclopropane. This higher boiling point would greatly simplify the liquefaction and packaging procedures; thus, if the liquefaction were to be done by means of pressure much less would be required or if it were to be done at normal pressures much less expensive refrigeration would be necessary. Ice brines for example would be sufficient refrigeration to liquefy methyl cyclopropane at atmospheric pressure. Moreover due to this higher boiling point the container in which it is distributed would not need to withstand more than very moderate pressures and therefore the design and construction of the container could be greatly simplified.

During the spring of 1933 we prepared a quantity of methyl cyclopropane by the reduction of 1,3-dibromobutane with zinc in a medium of 85% alcohol. This was essentially the method of Demjanow (1) excepting, of course, that we modified this method according to the principles already described (2, 3) for the improvement of the yields in reactions of this type, the restraint of side reactions therein and the purification of the gaseous products so that they would be suitable for use as inhalation anesthetics. Thus, in the production of methyl cyclopropane[2] by this reaction,



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* Scientific Section, A. PH. A., New York meeting, 1937.

[1] Research Department of the Chemical and Pharmaceutical Laboratories, E. R. Squibb and Sons, Brooklyn, New York.

[2] Complete experimental details have previously been described by Lott and Christiansen in the preparation of cyclopropane and propadiene (*loc. cit.*)

the 85% alcohol which was the reaction medium was kept in a vigorous state of agitation during the addition of the zinc dust, and in a vigorous state of ebullition and agitation throughout the gradual addition of the 1,3-dibromobutane. The gaseous methyl cyclopropane was thoroughly scrubbed using activated carbon to remove vapor impurities by adsorption. A yield of 81% of liquefied methyl cyclopropane was obtained by refrigeration and the product characterized by means of the following determinations:

B. p.: 2–5° C., largely 4–5° C.	Recorded 4–5° C.
Molecular weight (Dumas method) 52.2	Theory 56
Assay (H_2SO_4 absorbable): 99.0%	
% isobutylene (bromine titration): 0.68%	

This material was subjected to test as an inhalation anesthetic in monkeys and is compared to cyclopropane from this point of view in the second section of this paper.

At a somewhat later date it occurred to us that we might be able to effect a reduction of the commercially available 1,3-dichloroisobutane with zinc to give methyl cyclopropane.

$$CH_3—CH\begin{matrix}CH_2Cl\\CH_2Cl\end{matrix} + Zn \rightleftharpoons CH_3—CH\begin{matrix}CH_2\\CH_2\end{matrix} + ZnCl_2$$

However, using the same reaction conditions as in the preparation[1] of methyl cyclopropane from 1,3-dibromobutane we obtained practically pure isobutylene. From 900 Gm. of 1,3-dichloroisobutane we obtained 150 Gm. of isobutylene, or 38% of theory. This gas was characterized as isobutylene by means of the following determinations:

B. p.: −6° C. Recorded for isobutylene: −6° C.
Molecular weight: 56. Theory: 56
Absorbable in H_2SO_4 (methyl cyclopropane and isobutylene): 100%
Bromine titration (isobutylene): 98.3%

The product from the dichloroisobutane was further characterized by means of its bromine derivatives.

Merezkosky (4) reported that pure isobutylene reacts with bromine to give a mixture of bromine derivatives of which 62% is isobutylene dibromide and 38% is tribromoisobutane when the temperature is uncontrolled and the reaction mixture allowed to become hot—in the cold the proportion of isobutylene dibromide is considerably larger and the proportion of tribromoisobutane correspondingly smaller. Using the method of Merezkosky we passed 20 liters of our gaseous product through 152 Gm. of bromine dissolved in twice its volume of chloroform in a flask provided with external cooling to maintain the reaction mixture at −15° to −19° C. Only 0.7 liter passed through the bromine unabsorbed. The chloroform solution of the bromine derivatives, after washing and drying, was repeatedly rectified until it was separated into two fractions which were shown to be isobutylene dibromide and tribromoisobutane.

Weight.	Per Cent of Total Brominated Material.	Boiling Point. Found.	Boiling Point. Literature.	Specific Gravity at 20° C. Found.	Specific Gravity at 20° C. Literature.
124.5 Gm.	84.3%	144–150° C.	147–8° C.*	1.760	1.759*
23.3 Gm.	15.7%	105–112° C/17 mm.	108–9° C/18 mm.**	2.198	2.197**

* Recorded for isobutylene dibromide.
** Recorded for tribromoisobutane.

[1] For experimental details see the papers on Cyclopropane and Propandiene by Lott and Christiansen previously referred to.

Thus we have obtained approximately the same kind and proportion of bromine derivatives with our sample of gas as Merezkosky obtained with his sample of isobutylene under strictly comparable conditions. We therefore can conclude that the gas is practically pure isobutylene containing methyl cyclopropane in an amount ranging from a trace to an upper limit of 1.7%. It should be noted that 1,3-dibromoisobutane in substantially the same reaction is known to give largely methyl cyclopropane (5) contaminated with some isobutylene, *i. e.* the same results as those obtained by using 1,3-dibromo normal butane.

In considering the behavior of the several chloro and bromobutanes it is interesting to recall that under conditions which with 1,3-dibromopropane give high yields of a gas consisting almost entirely of cyclopropane, 1,3-dichloropropane is only slightly reactive, giving a low yield of gas which has a quite considerable propylene content. The results obtained with the several dihalopropanes and dihalobutanes under our experimental conditions are summarized in the following table.

Starting Material.	Total Yield.	Composition of Product. Cyclic.	Olefinic.
1,3-dibromo (*n*) butane	High	99.3	0.7
1,3-dibromo (*iso*) butane	High	Large	Small
1,3-dichloro (*n*) butane	Not investigated		
1,3-dichloro (*iso*) butane		1.7	98.3
1,3-dibromo propane	High	ca 100	Practically none
1,3-dichloro propane	Low	Some	Some

We realize that at the A. C. S. meeting in Florida (Spring of 1934) Hass and McBee reported that cyclopropane can be made satisfactorily and cheaply from 1,3-dichloropropane. Their reaction conditions were not disclosed until the Pittsburgh meeting of the A. C. S. (Fall of 1936) (6). In order to get these results with dichloropropane certain special conditions had to be used. In considering our data on the behavior of the chloro and bromo propanes and butanes it should be kept in mind that special conditions were not used with the chloro compounds; their behavior under conditions giving good yields of the cyclic hydrocarbon from the bromo compounds was determined. Perhaps by means of the special conditions used by Hass, *et al.*, for 1,3-dichloropropane it would be possible to obtain methyl cyclopropane instead of isobutylene from the dichlorobutanes.

Although we would hesitate very much to discuss the mechanism of these differences in rates and direction of reaction on a basis of so little evidence it may not be too venturesome to suggest that there are under the conditions of our reactions two potential changes possible, *viz.* (1) tendency for 1,3-dihalides to change to the more stable isomers, the 1,2-dihalides, and (2) tendency for reduction by removal of two halogens by means of zinc. Furthermore it is known that this loss of two halogens is incurred more rapidly by a 1,2-dihalide than by a 1,3-dihalide, *i. e.*, the formation of propylene from 1,2-dibromopropane is much more rapid than the formation of cyclopropane from 1,3-dibromopropane. Thus it is suggested that the lower total yields of gas, and the higher olefine content obtained from dichlorides is due to the act that the tendency to lose two chlorine atoms is much less than to lose two bromine atoms so that with the chlorine com-

pounds the rearrangement to the 1,2-dihalide followed by loss of two halogens and formation of an olefine proceeds more rapidly than loss of two halogens from the 1,3-dihalide to give a cyclic hydrocarbon. The meager evidence available also suggests that probably the rearrangement of the isobutane 1,3 dihalide to the 1,2-dihalide is more rapid than in the case of the normal butane 1,3-dihalide.[1]

II. Anesthetic Properties of Methyl Cyclopropane.

BY L. F. SHACKELL.

Cyclopropane.—The results of an extended study of cyclopropane anesthesias in monkeys have been published by Shackell and Blumenthal (7). In this study it was found that 17 or 18 per cent of cyclopropane in an anesthetic mixture was sufficient to induce a surgical degree of analgesia with complete muscular relaxation. There was moderate dilatation of the pupils. Salivation was relatively slight. Urine was voided one or more times within an hour after removal of the mask. Consciousness was regained within 1 to 3 minutes after removal of the mask. Heart and respiratory rates in the monkey are depressed by cyclopropane. This was discussed in detail by Shackell and Blumenthal. In Table I have been collected the mean values for heart and respiratory rates of three monkeys which have been used more recently in numerous tests of cyclopropane as well as in the tests of methyl cyclopropane described below. In Table I the highest concentration of cyclopropane for a given monkey would have proved fatal within a few minutes if the mask had not been removed.

Table I.—Mean Values for Heart and Respiratory Rates of Rhesus Monkeys during Anesthesias with Cyclopropane at Various Concentrations.

Cyclopropane %.	Heart Rate.	Respiratory Rate.
	Monkey LH, Female, 4.5 Kg.	
0	196	42
18.7	185	27
22.2	182	26
27.4	183	23
31.8	169	22
	Monkey LS, Female, 5.1 Kg.	
0	199	42
18.2	164	43
22.6	162	41
27.0	161	29
	Monkey RS, Male, 9.7 Kg.	
0	184	40
18.0	145	35
22.7	142	36
26.5	127	29

Anesthesias with cyclopropane are free from the tremors and convulsive seizures that characterize the actions of ethylene and propylene. Repeated

[1] This would be based solely on Faworski's work. It would be interesting to attempt the preparation of methyl cyclopropane from 1,3-dichloro *n*-butane.

anesthesias, even at sublethal concentrations of cyclopropane, apparently cause no damage to the monkey. Three of these animals, more than four years after they were used in the experiments reported by Shackell and Blumenthal, are being subjected to occasional anesthesias in control tests of cyclopropane.

Methyl Cyclopropane.—The three monkeys, LH, LS and RS, referred to in Table I in connection with tests of cyclopropane, were subjected to two anesthesias each with methyl cyclopropane. The first anesthesia in each monkey was at, or somewhat above, the threshold for surgical anesthesia; while the second anesthesia was carried out at increasing concentrations until a sublethal, or at least dangerous, level appeared to have been reached. Following is a summary of the experimental findings:

1. Induction of anesthesia is rapid and is accompanied by relatively little struggling.

2. During induction, and ordinarily after each addition of methyl cyclopropane to the anesthetic mixture, the monkey exhibits involuntary tremors, jerks or generalized convulsive seizures that are strikingly similar to those caused by ethylene and propylene. In contrast with propylene, however, these spasmodic reactions usually persist for only a few minutes. As was pointed out above, such side-effects have not been observed with cyclopropane.

3. The concentrations of methyl cyclopropane and of cyclopropane required to produce complete relaxation appear to be nearly the same, namely, 16 to 18 per cent. The lethal concentrations of the two gases also are nearly the same. The mean lethal concentration of methyl cyclopropane for the three monkeys was 27.7 per cent, while a like value for cyclopropane was 28.4 per cent.

4. It has been shown above that cyclopropane depresses both heart and respiratory rates in the monkey. With methyl cyclopropane the heart rate tends to be slowed; but individual monkeys vary in this respect, especially at different methyl cyclopropane concentrations. The respiratory rate under methyl cyclopropane, however, shows definite acceleration.

Typical data for heart and respiratory rates at different methyl cyclopropane levels are given in Table II.

TABLE II.—MEAN VALUES FOR HEART AND RESPIRATORY RATES OF RHESUS MONKEYS DURING ANESTHESIAS WITH METHYL CYCLOPROPANE AT VARIOUS CONCENTRATIONS.

Methyl Cyclopropane %.	Heart Rate.	Respiratory Rate.
	Monkey LH, Female, 4.5 Kg.	
0	200	34
16.8	185	32
28.4	196	88
	Monkey LS, Female, 5.1 Kg.	
0	205	41
15.8	219	52
22.2	200	67
26.5	253	80
	Monkey RS, Male, 9.7 Kg.	
0	186	34
14.8	163	52
28.2	160	50

5. Salivation is slight with both methyl cyclopropane and cyclopropane. Vomiting has not been observed after either anesthetic.

6. Post-anesthetic depression and loss of appetite appear to be more marked after methyl cyclopropane than after cyclopropane.

SUMMARY.

Methyl cyclopropane has been prepared in a condition of purity suitable for its evaluation as an inhalation anesthetic, by the reduction of 1,3-dibromobutane with zinc. The reduction of 1,3-dichloroisobutane under similar conditions gave almost entirely isobutylene instead of methyl cyclopropane.

Although the effective concentrations as well as the lethal concentrations of methyl cyclopropane and cyclopropane, and hence their margins of safety, are about the same, the methyl cyclopropane does not compare favorably with cyclopropane in a qualitative and quantitative comparison of their several side-effects.

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(7) Shackell and Blumenthal, *Anesthesia and Analgesia*, 13, 133 (1934).

A PRACTICAL METHOD FOR TESTING NON-PHENOLIC DISINFECTANTS.*[1]

BY WILLIAM C. CLARK.

Jordan (1) defines a disinfectant as a substance that kills the microbes with which it comes into contact. This statement is a very broad and general definition and Reddish (2) clarifies this general statement by asking "What are disinfectants for and why are they used?" and answering "Disinfectants are germicides which are used on inanimate objects for the purpose of killing disease germs which cause epidemiologic diseases. Their primary purpose is to aid in preventing the spread of disease by killing the bacteria which cause them."

Varley (3) recognizes the limitations of the Phenol Coefficient Method and proposes a method for testing disinfectants which are chemically related to Phenol that closely simulates the conditions of use of these disinfectants. His method is adapted to testing odorous disinfectants which may be washed away after a relatively short time. A simpler method was desired for an odorless non-phenolic disinfectant that is recommended for disinfecting floors, woodwork and furniture in the sickroom. Because this disinfectant is colorless and odorless it is not removed from the woodwork by washing, but remains on the wood until the next regular washing of the woodwork.

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* Scientific Section, A. Ph. A., New York meeting, 1937.

[1] A contribution from the Bacteriological Laboratory of James F. Ballard, Inc.

In devising this test the object was to have the conditions of the test as nearly identical as possible with the conditions of use in the sickroom.

Materials needed for this test are available in any bacteriological control laboratory and are as follows:

Three varnished sticks 8 x 4 x 100 mm. Three painted sticks of the same dimensions. These sticks are cut to the above dimensions and are dipped into the varnish or paint and then allowed to dry one week or longer. Strips of linoleum or other floor coverings having the same dimensions may also be used. One lot of tubed nutrient broth, each tube containing 10 cc. of nutrient broth made and sterilized as directed in Circular 198 of the United States Department of Agriculture (4).

One large pair of forceps such as is used in plugging tubes with absorbent cotton.

One culture of *Straphylococcus aureus* 22 to 26 hours old and meeting all the other requirements of Circular 198 of the United States Department of Agriculture.

Six sterile medication tubes 25 x 150 mm. plugged with absorbent cotton before sterilization.

The Test.—Mark one end of each stick by any suitable means and grasp the opposite end in the left hand. Sterilize the marked end of the stick by passing it through the flame. Take the forceps in the right hand, flame the tips and grasp the marked end of the stick with forceps and flame the entire stick and the lower end of the forceps. Allow the stick to cool a few seconds, place the stick into the culture and stir it about 15 seconds. Remove the stick from the culture and place it on a recently flamed and cooled wire gauze. The entire operation should be performed using the usual aseptic precautions. Repeat the above operation with the five remaining sticks. Allow the six sticks to remain on the wire gauze exposed to the air just as is the woodwork in a sickroom.

After 72 hours have elapsed completely immerse each of the inoculated sticks into the highest dilution of the disinfectant that is recommended for disinfecting woodwork in the sickroom. Keep each stick completely immersed in the diluted disinfectant for thirty seconds. Transfer each stick from the diluted disinfectant into a dry, sterile, medication tube. Flame the mouth of each medication tube and replace the cotton plugs. Invert each medication tube after the sticks are in the tubes and the cotton plugs have been replaced. The object in inverting the medication tube is to permit the cotton plug to absorb any excess liquid and to permit the stick to dry rapidly. Allow the medication tubes to remain inverted for one hour.

With sterile forceps remove a stick from a medication tube and place it into a tube of sterile broth marked number one. Stir the broth for thirty seconds and then transfer the stick to a tube of sterile broth marked number two. Stir thirty seconds and remove the stick. This operation is repeated with the five remaining sticks. Aseptic precautions must be strictly observed in this part of the test to prevent the possibility of contamination. Incubate all twelve of the tubes of broth for 48 to 72 hours. Examine the tubes for growth. The object of the second subculture is to render the disinfectant too dilute to inhibit the growth of *Straphylococcus aureus*.

If growth occurs in all of the second subculture tubes, the dilution of the disinfectant used in this test has failed to kill the test organism.

If growth occurs only in one or two of the second subculture tubes, contamination may have occurred. Make an agar slant streak, incubate 24–48 hours and examine. If the organism is not *Staphylococcus aureus*, contamination has occurred. If the organism proves to be *Staphylococcus aureus*, the test must be repeated, as this organism may or may not be a contamination.

If no growth occurs in any of the second subculture tubes, the disinfectant has killed the test organism under conditions which are as nearly identical as possible to the conditions of use in disinfecting the woodwork of a sickroom. If there are any reasons to suspect that inhibition and not killing has occurred, inoculate the six tubes that are marked number two and incubate 24 hours. Growth proves that no inhibition has occurred.

In the disinfection of woodwork, the concentration of the disinfectant begins to increase immediately as the water evaporates; this increase in concentration continues until practically all of the moisture has evaporated. As a matter of fact, the bacteria will remain in contact with the disinfectant until it has decomposed or evaporated. The time of exposure of the bacteria to the disinfectant will, of course, vary with each different disinfectant; therefore, a fifteen-minute exposure in no way approximates the time of exposure in this use of the disinfectant. As a rule the temperature of a sickroom is above 20° C. These three fundamental conditions—concentration of the disinfectant, time of exposure of the bacteria to the disinfectant and temperature at which the bacteria are exposed to action of the disinfectant—are conditions which must be observed in any test that purports to give a true indication of the value of a disinfectant.

Considering these wide variations in conditions, it is readily apparent that the Phenol Coefficient Determination is not well adapted to the testing of claims for a non-phenolic disinfectant for use on the woodwork in a sickroom. A disinfectant which can be diluted only as much as one part of disinfectant to three parts of water in order to kill *Staphylococcus aureus* within five minutes using the Phenol Coefficient Determination shows effective disinfection by killing the same culture when one part of disinfectant is added to ten parts of water by this method of testing!

Such a variation in the concentration of the disinfectant required to kill a standard strain of *Staphylococcus aureus* is to be expected under such wide variations in conditions as exist between the Phenol Coefficient Determination and the disinfection of woodwork in a sickroom. The end sought in the disinfection of woodwork is the death of the bacteria by the disinfectant; not necessarily the killing of an extremely large number of bacteria in a few minutes. It is of no material difference whether the bacteria are killed in five minutes or in several hours; disinfection has been accomplished.

There are several factors that give this test a reasonable margin of safety. The fact that *Staphylococcus aureus* is a more highly resistant organism than *E. typhi*, the official test organism used in the Phenol Coefficient Method, the fact that the disinfectant remains on the woodwork for a much longer period of time than the time of the test, and the presence of the organic matter in the test materials, offer a reasonable margin of safety for this test.

Naturally this test has very definite limitations and these limitations must be observed if this test is to be of value. This test is limited to the use of testing non-phenolic disinfectants which do not depend on a volatile constituent and which are odorless. The disinfectant must not be washed off the woodwork for several days.

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THE NECESSITY FOR A SPECIFIC COURSE IN BACTERIOLOGY FOR PHARMACY STUDENTS.*

BY FANCHON HART.[1]

With the exception of a few notable cases, two extremes appear to characterize most of the bacteriology curricula as presented in the different colleges of pharmacy. One type of curriculum follows much too closely the medical bacteriology, in that it includes the cultivation of the pathogenic organisms, the preparation of vaccines, the collection of body-fluids including the spinal-fluid and the blood.

The time allotted to a course in bacteriology in a pharmacy school and the educational background of the student, is rarely adequate for this type of work. The other form of instruction is largely that of a botanical nature with little consideration of the biologicals so important to pharmacy.

The course in bacteriology should be so planned as to objectives that the graduates from our schools could use it as a basis for further study in bacteriology or related fields, if they so desire.

It is the function of the pharmacist to keep in close touch with all the medicaments on the market, including the particular advantages of each, usually expressed in the advertisement. His comprehension of the biological literature nevertheless will be largely dependent upon his previous training at college.

It is my belief that physician and pharmacist might meet here on common ground. In no other part of his work does the pharmacist have as great an opportunity to coöperate with the physician and by so doing thus gain his confidence. This is still, I believe, the cherished dream of the pharmaceutical profession as a whole.

The training at college should be of such a nature that the student will understand readily the differences between the various types of biologicals, their composition, methods of manufacture, the standard tests for potency and sterility, the necessity for an expiration date and other related details. Fortified with a basic knowledge of the Official Biologicals, it is to the pharmacist's advantage to acquaint himself with the commercial variants as well as with the newer preparations as they appear on the market. The much "detailed" physician often seeks the unprejudiced advice of an intelligent and well-informed pharmacist. Emphasis should therefore be placed on a thorough knowledge of the biologicals.

Second in importance in a bacteriological curriculum for pharmacy students is an objective, the results of which will appeal to the ethically minded members of the profession. I have in mind the thorough training in bacteriological technique. But it must be impressed upon the student that under no conditions should an individual with training solely from a school of pharmacy attempt to give advice, diagnose the disease or in any manner interpret the results of his findings.

The technique involved in operations such as the chemical analysis of the blood and urine, total and differential blood counts, the microscopy of urine samples, the staining of throat, sputum and smears from purulent exudates could easily be

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* Section on Education and Legislation, A. PH. A., New York meeting, 1937.

[1] Associate Professor, Materia Medica. College of Pharmacy, Columbia University, New York City.

handled by the pharmacist. However, the finished slides should be examined by the physician, unless the pharmacist has had an advanced course and license to examine specimens of this kind. The busy and anxious physician might welcome the service of a competently trained person.

The small group of laboratory technicians, who might suffer slightly from this procedure is as nothing compared to the immense number of patients who would gain by a more thorough investigation if the laboratory routine were to start with the first visit to the physician's office. The smear, culture tube or blood sample may be taken to the pharmacist with the prescription by the patient. In many cases this method would prove to be a valuable saving in time. There have been complaints of the methods of distribution and collection of material to and from Health Department stations in large cities, with just criticisms of possible faulty diagnoses because of unavoidable delays.

Finally the third objective is of the greatest importance from the viewpoint of the health of the community. Nowhere are we given so fine an opportunity in which to deal with personal and mass hygiene and sanitation. Lessons in cleanliness and the results of contamination may be interestingly demonstrated by tests for the sterility of eye lotions and intravenous solutions, including those in ampuls. The subject matter should include the knowledge that will assist the future pharmacist to meet and honestly discharge the duties that the public has a right to demand of him, duties not of a pharmaceutical nature but rather those of every intelligent citizen with the educational experience that must motivate the desire for the betterment of human welfare.

The course should include the mechanism of immunity and the control of the common communicable diseases, as well as the incubation periods and the diseases that are under quarantine regulations and therefore reportable to the local authorities. A knowledge of the manifestations of the common diseases causing skin eruptions is of great value, particularly in the more congested areas of the larger cities. The pharmacist should be acquainted with the local health regulations, including the regulations governing milk and water supplies. He should have a knowledge of the inspection, sterilization and dangers of infection from swimming-pools, community drinking cups, lavatories and improperly handled and stored food-stuffs. He should know how the city sewage is disposed of and what possible diseases might be conveyed through the improper or total lack of the disposal of waste.

Many interesting projects easily motivate the student toward active participation in gathering data on this subject.

Each objective may be built upon in such a manner as to give advanced instruction for specialized fields of service.

The first objective might well be an introduction to an advanced course for bacteriologists in the field of biological research. The subject matter is also particularly valuable as sales information for those wishing to engage in detail work for the manufacturer of bacteriological biologicals.

The second part of the course is a prerequisite for more detailed work required of the hospital clinician, private laboratory technician and medical or dental assistant.

The third objective of the curriculum opens up the possibility of civil service

employment. The basic knowledge mastered in this course may stimulate a desire to seek positions in Health Department work, particularly in the inspection of food, water and milk.

The course would not be complete without the necessary information concerning veterinary biologicals. They are becoming increasingly more important. The alert pharmacist may well find it an asset to feature these preparations as attractive displays with such information as would be both interesting and pertinent to the material on exhibit.

OUTLINE FOR A COURSE IN BACTERIOLOGY FOR PHARMACY STUDENTS.

INTRODUCTION

- Historical data
  - Contributors
  - Theories of disease
- Fundamental considerations
  - Subject matter
    - Sanitation and the Health Department Sanitary Code
    - Sterilization
    - Disinfection
    - Antisepsis
    - Fumigation
    - *Microörganisms
      - Bacteria
      - Viruses (of unknown origin)
      - Molds
      - Protozoa
      - Metazoa.

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* Under each of the above group of organisms the following points are to be considered—staining technique, cultivation, morphology and classification. Only non-pathogenic material is to be handed out to the student. The student should be required to examine smears from his own throat. Demonstrations are to be set up for observation. The purpose being to familiarize the student with the appearance of the pathogenic organisms and the more important serological reactions.

- Useful microörganisms
  - Of economic importance in
    - Agriculture
    - Dairy industry
    - Bakers' supplies
    - Fermentation products
    - Citric acid production
    - Dye industry
    - Fabric manufacture
- Harmful microörganisms
  - Soil contaminants
  - Food contaminants
  - Water contaminants
  - Organisms causing spoilage of drugs and drug products
  - Organisms causing wood rot
  - Animal parasites
    - Flukes, tapeworms, hookworms
    - Agents of infection and infestation
- Biological products, types of
  - Biologicals official in the U. S. P.
    - Composition
    - Methods of preparation
    - U. S. P. H. S. control
    - Standardization
      - Tests for potency
      - Tests for sterility
    - Labeling, regulations
    - Packaging
  - Biologicals, unofficial
    - Differences between the commercial types
    - Vaccines
    - Bacterial antigens
    - Sero-bacterins
    - Immunogens
    - Phylocogens
    - Opsonogens
    - Aggressins

Modified viruses
Anti-bacterial sera
Antibody solutions
Antitoxins
Toxin-antitoxin
Toxoids
Antivenin
Tuberculins
Mallein
Johnin
Pollen extracts
Protein extracts
Diagnostic reagents
Mechanism of immunity
Natural
Induced
Complement fixation
Widal reaction and other specific serum reactions
Regulations concerning the storage
Date of expiration
Keeping qualities

The unit covering *Sanitation*, includes the disposal of waste and sewage: the treatment of water supplies, milk and food inspection and other regional regulations.

Under *sterilization*, the special treatment for Galenicals and other medicinal substances, including *prescriptions* is emphasized. The various sterilization and pasteurization methods should be freely illustrated by each student.

Since the most important objective of this course is to acquaint the student of pharmacy with the official biologicals and commercial products of a related nature, he should be as familiar with the composition, use and dosage of these preparations as with any topic in Materia Medica.

Because of the frequency with which our graduates find positions in the technical, clinical or commercial laboratory it has become increasingly more important to include simple bacteriological technique in our curriculum.

A COURSE IN LABORATORY GLASS BLOWING IN A COLLEGE OF PHARMACY CURRICULUM.*

BY HORACE M. CARTER.[1]

Comparatively few schools and colleges in the United States, at the present time, offer courses in laboratory glass blowing. The foreign universities, on the other hand, have apparently long recognized the practical value of adequate training in glass manipulation, a most necessary adjunct to the person properly qualified to enter the field of chemical research.

There are, no doubt, a certain number of our American universities which provide a training in glass manipulation, but I am aware at the moment of only one of our leading technical institutes which *requires* a course in laboratory glass blowing of its undergraduates in chemistry. The majority of the universities prefer to maintain a department under the supervision of an expert glass blower for the repair and construction of glass apparatus. The chemist who ultimately enters the research field without any practice in the technique of glass manipulation finds himself entirely helpless to make repairs or to construct the simplest type of apparatus.

Many laboratories which specialize in the preparation of synthetic organic chemicals, and many industrial firms which maintain a research department, re-

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* Section on Education and Legislation, A. PH. A., New York meeting, 1937.

[1] Associate Professor of Pharmacy, Columbia University, College of Pharmacy.

quire their chemists to design and prepare all of the types of special glass apparatus required in research. The Eastman Kodak Company, in an interesting booklet entitled, *The Preparation of Synthetic Organic Chemicals at Rochester*, states:

"All special apparatus, from distillation flasks to the more complicated pieces, are prepared from Pyrex glass by the chemists who design and use them." The book abounds with illustrations of special apparatus, not commercially available, designed by Eastman chemists.

The commercial manufacturers of glass and glassware are apparently aware of the fact that those engaged in chemistry have had little or no practical experience in glass blowing. These manufacturers are moreover aware of the need of instruction in this field, and because of the lack of adequate instruction provided by the colleges and the universities, have taken it upon themselves to prepare booklets giving directions for the fabrication of glass apparatus. The Corning Glass Works, in a most valuable booklet, "Pyrex Bends, Bulbs and Seals," states:

"To aid laboratory workers in their efforts to become adept apparatus builders, Corning Glass Works offers, herewith, some suggestions as to the proper tools and equipment as well as the correct procedure in the construction of 'PYREX' apparatus."

This book also is replete with illustrations and should prove a most valuable aid to the amateur worker.

In view of the fact that the designing and fabrication of apparatus plays a most important rôle in the realm of chemistry, I have long felt the need of the inclusion of a course in laboratory glass blowing in the curriculum of those schools and colleges which prepare men to engage in chemical research.

Many of the colleges of pharmacy in the United States for the past number of years have been sending men into the research field of the pharmaceutical and allied professions. I am of the opinion that these men would be greatly benefited if, in the course of their studies, there was provided systematic instruction in laboratory glass manipulation.

It is understood that such a course in laboratory glass blowing has not as its aim the training of professional glass blowers; its object is to offer adequate instruction which will enable the worker to become proficient in carrying out the most common and most frequently used operations involved in the construction of laboratory apparatus.

It naturally follows that the first exercises be simple, at the same time stress fundamental points, such as the rotation of the glass, the proper working temperature, simple bends, drawing out a tube, constricting a tube, flanging a tube, which operations must be fully mastered and amplified later.

Then may follow the simple exercises of joining tubing of the same diameter, joining tubing of different diameters, construction of the "tee" tube, blowing a bulb on the end of a tube and blowing a bulb in a tube.

With these fundamentals as a foundation, the actual construction of apparatus may be attempted, *e. g.*, sealing a tube through another tube, required in making a gas-washing bottle, a suction pump or a Kjeldahl trap. Further practice in making ring seals and spirals, together with the fundamental operations already attained, will enable the worker to construct a variety of apparatus. In addition, one may purchase from the manufacturers of laboratory glassware, certain forms and sizes of flasks, stop-cocks, ground joints, etc., which may be utilized in the construction of special designs.

Our attention need hardly be directed to the fact that the Departments of Pharmacy, Chemistry and Materia Medica offer a wealth of material for the duplication, repair and construction of standard or special apparatus.

EXTRACTION OF NUX VOMICA IN THE MAKING OF TINCTURE.*

BY NELLIE PERRY WATTS.[1]

When the Tincture of Nux Vomica, manufactured according to the directions of the United States Pharmacopœia, Eleventh Revision, came upon the market, great indeed was the consternation. For decades this tincture had been an amber solution; the new product, however, is a red liquid. Not only is it red, it is of different shades of red; the products of the various manufacturers differ in shade, and even one lot of a manufacturer may vary from his next lot. You well know the doubt this change in color causes in the minds of the retail and dispensing pharmacists, particularly in the refilling of prescriptions calling for this galenical.

The formula for preparing the Tincture of Nux Vomica has changed many times. In reviewing its history in this country it will be found that until the Third Revision in 1851 the crude drug (nux vomica) only was official. In the revision of 1851 the tincture was directed to be made from the rasped seed, using eight ounces to two pints of finished tincture. The drug could be macerated, or macerated and later percolated, with the then official alcohol, specific gravity 0.835, which was about 90 per cent by volume. A menstruum of alcohol, too, yields an amber-colored tincture. For several decades no changes were made in this preparation, other than that the rasped drug was replaced by a fine powder. In the Sixth Revision, among other changes the menstruum was diluted—eight parts of alcohol to one part of water. It was in 1890, the Seventh Revision of the Pharmacopœia, that acid was first introduced; and extract of nux vomica was made from 1000 Gm. of drug, 50 cc. of acetic acid, 750 cc. of alcohol and 250 cc. of water. The tincture was made by dissolving sufficient of the extract in a mixture of alcohol and water (3:1) to have a concentration of 0.3 per cent of alkaloids. In the Ninth Revision (1910) the tincture was again made by percolating the drug without acid; in 1920 the process was continued with the addition of acetic acid. In the Eleventh Revision the 10 cc. of acetic acid per 100 Gm. of drug was replaced by 7.5 cc. of hydrochloric acid.

Nux Vomica seeds contain the alkaloids strychnine and brucine combined with igasuric acid, an acid similar to tannic acid. There is also present a glucoside —loganin (1).

In a study of this tincture five experimental lots were prepared; in each instance 100 Gm. of nux vomica, ground to a moderately coarse powder, was packed in a glass percolator and, after being moistened with the menstruum for twenty-four hours, drained at a rate of 3 to 5 drops per minute. Percolation was continued until the tincture measured 1000 cc. The menstrua used were:

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* Section on Practical Pharmacy and Dispensing, A. PH. A., New York meeting, 1937.

[1] Philadelphia College of Pharmacy and Science.

1. Alcohol, 3 parts, distilled water, 1 part.
2. Alcohol, 150 cc.; distilled water, 42.5 cc.; hydrochloric acid 7.5 cc. Completed with alcohol, 3 parts; distilled water, 1 part.
3. Alcohol, 150 cc.; distilled water, 45 cc.; hydrochloric acid, 5 cc. Completed with alcohol, 3 parts; distilled water, 1 part.
4. Alcohol, 150 cc.; distilled water, 40 cc.; hydrochloric acid, 10 cc. Completed with alcohol, 3 parts; distilled water, 1 part.
5. Alcohol, 750 cc.; distilled water, 240 cc.; acetic acid, 10 cc. Completed with alcohol, 3 parts; distilled water 1 part.

The drug moistened by menstrua numbers 1 and 5 was of a gray color, while that moistened by numbers 2, 3 and 4 was of a pink shade. In all cases practically all of the heavily colored portion of the tincture was to be found in the first 200 cc. of the percolate. In the filtering of these percolates, after chilling them at 5° C. over night, tincture number 1 filtered easily, number 5 the next easily and the three containing hydrochloric acid with difficulty. This was true when an ordinary funnel was used and also when a Büchner was employed. The finished tinctures 1 and 5 were amber liquids, while numbers 2, 3 and 4 (those containing hydrochloric acid) were red.

When these tinctures were assayed for their strychnine content, all were found to come within the Pharmacopœial range of 0.108 to 0.120 per cent. Number 2 (U. S. P. XI) gave a slightly higher yield; numbers 1, 3 and 5 were of practically the same strength; and number 4 (10 cc. of hydrochloric acid) was shown to be slightly weaker than the others.

In a total solids assay, in which 10 cc. of each tincture was evaporated to dryness at 100° C., the U. S. P. XI product gave the most residue. Of more interest than the weight, however, is the nature of this residue. In the cases where hydrochloric acid had been in the menstruum a black residue with a tarry or phenolic odor resulted, while an amber-color residue almost lacking in odor resulted when hydrochloric acid was not used.

Why is the tincture official at present red? As a possible explanation I offer that the glucoside loganin is hydrolyzed in the presence of the hydrochloric acid, yielding glucose and a red substance. In the literature it is recorded that loganin turns red in the presence of sulfuric acid (2). The ground nux vomica turns pink when moistened with sulfuric acid and with hydrochloric acid, but not with acetic acid.

By the use of Fehling's solution to detect the presence of glucose, and in turn the hydrolysis of a glucoside, it was found that in tinctures 1 and 5 no reduction occurred, while in the tinctures containing the hydrochloric acid the Fehling's solution was reduced.

The method of preparation of this tincture is now before the Committee of Revision of the United States Pharmacopœia. In a *Bulletin*, dated August 13, 1937, a paragraph referring to this tincture reads:

"The Contact Committee and others believe the U. S. P. X acetic acid menstruum should be reinstated as the new hydrochloric acid menstruum produces color and other changes."

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PROBLEMS OF THE HOSPITAL PHARMACY.*

BY S. W. MORRISON.[1]

It is of vital importance to the progress of Pharmacy that the hospital pharmacy be maintained on a high level, for it is there that the young doctor first makes contact with the pharmacist and gathers his first and most lasting impressions of him and his profession. In the hospital, the doctor consults and works with the pharmacist more than he does in the average retail store.

In general, the pharmacist does not receive the recognition and consideration due him by the managers and superintendents of hospitals. In many instances there is insufficient help, lack of proper equipment and a poor location. This condition may be due to several factors; an incompetent pharmacist, lack of funds or lack of information by the superintendent regarding the importance and the needs of the pharmacist.

There is a growing tendency to take the purchasing of drugs and certain hospital supplies away from the pharmacist and to place it in a central service station. It is important that the pharmacist assert himself and keep the purchasing and handling of drugs under his control.

In order to make your services most valuable, it is necessary that the medical staff be informed and advised regarding new preparations in stock and in the use of U. S. P. and N. F. preparations. An adequate library should be required in every hospital pharmacy where information concerning any medical preparation may be obtained. The doctors and interns are always eager to receive suggestions and information pertaining to drugs or prescription writing.

To control the stock and eliminate undesirable proprietaries which may be duplicates of another similar preparation, the pharmacist should meet with the various departmental staffs and discuss with them what preparations are most desirable and needed and to recommend U. S. P. and N. F. galenicals whenever possible. By so doing a smaller variety of drugs will be needed, the cost of medication will be decreased and there will be less dead stock on the shelves.

The pharmacist should be prepared to decide upon the merits of a drug and should be equipped to assay them when necessary to determine the quality. He should also be the one to buy the drugs or at least to specify what shall be purchased.

The restrictions placed on the doctor in limiting the type or number of drugs or the form of administration should not exist, except to eliminate as much as possible the proprietary drugs which are duplicates of U. S. P. or N. F. preparations.

It is our policy at Illinois Research Hospital to permit the doctor to prescribe any form of medication that he wants. By doing so he is more impressed with your ability and your desire to be of service and learns to write prescriptions requiring pharmaceutical compounding. Likewise, in a teaching institution such as ours, where the pharmacy students receive instruction and training in the hospital, it is highly desirable that the greatest possible variety of prescriptions be available for the students.

* Presented before the Sub-Section on Hospital Pharmacy, A. PH. A., New York meeting, 1937.

[1] University of Illinois, Research Hospital, Chicago, Ill.

Absolute cleanliness is imperative to proper recognition. Insist on a clean properly equipped drug room. Too often the drug room is not clean or inviting in appearance, balances and equipment are tarnished and soiled, and dirty utensils are allowed to accumulate.

You can render a very useful service by supplying the doctor with any special form of medication. If a doctor requests a particular substance in ampuls for hypodermic use, the pharmacist should be prepared to make such a solution. All intravenous solutions should be prepared or supervised by the pharmacist. Too often such solutions are purchased ready made or are made by some one in the hospital who is not a pharmacist.

Another essential to proper hospital service is to operate the pharmacy in an economical manner. Most hospitals operate on a very close margin and the lowering of costs is of vital importance. One way to lower costs is by manufacturing the galenicals needed in the hospital. I realize that many hospitals do not have sufficient help to manufacture many of the galenicals or intravenous solutions. In some cases added help can be justified by improving the service and by lowering the cost of medication. I know of a hospital that hired a pharmacist to manufacture preparations because he was able to show the manager how he could save considerably on the cost of drugs.

The use of intravenous dextrose solutions has increased to the extent that it becomes one of the major duties of the pharmacist to prepare these solutions. A 50% solution of dextrose is made using warm freshly triple distilled water and is then filtered through filter paper till clear. Filtration is rapid and this stock solution is then ready to make the 5% or 10% solutions as requested. A 40-oz. bottle with a bakelite cap is used. It is first washed with soap solution, rinsed thoroughly with water, then triple-distilled water to be sure that it is perfectly clean. Freshly triple-distilled water is used for making the solutions and the bottles are capped with parchment paper before sending to the autoclave. The solution is sterilized at 15-lb. pressure for 15 minutes. The cost of a 10% solution is 3¢ per liter (excluding labor) if made with Dyno, a brand of dextrose made by the Corn Products Co. Double-distilled water is satisfactory if properly distilled and used immediately. Another important precaution is the necessity of chemically clean rubber tubing and glassware. If desired the 50% solution may be sterilized at 5-lb. pressure for 40 minutes and kept for future use.

Ampuls of congo red, indigo carmine, isoiodeikon, procaine, sodium citrate, sodium iodide and others can all be easily made and at considerable saving. Washed, noncorrosive glass ampuls are filled with the solution by means of a large hypo needle attached to a burette. The ampul is sealed and then sterilized in the autoclave. In some instances the solution is put in rubber-capped serum bottles and sterilized.

Further economy may be effected by the use of bulk ether for anesthesia. We have used bulk ether U. S. P. XI in 27-lb. drums for over $2\frac{1}{2}$ years with very good results. Only once in that time have we had a drum of ether that could not be used for anesthesia. The ether is tested each time it is issued to the operating room, for acids, aldehydes and peroxides. The U. S. P. XI tests are used for the acids and peroxides. The sulfurous acid-fuchsin T.S. is used for the aldehyde test. The ether, if satisfactory, is put in $\frac{1}{4}$- and $\frac{1}{2}$-lb. cans tightly stoppered

with corks. The ether is quickly used and is never more than one week old. Bulk ether would not be recommended for small hospitals where the demand is less.

Since our hospital is a teaching institution, we also give the students instruction in tablet manufacture. Tablets of ephedrine, ephedrine and phenobarbital, sodium chloride, ammonia chloride, sodium acid phosphate, methenamine and some glandular tablets can be profitably made and with very little effort. We are equipped with a 3B Colton Tablet machine and wet granulator and it may be found practical for you to invest in a small tablet machine which can be purchased for as little as $75.00.

Our hospital is divided into departments, each one having a separate budget. The drug room operates on a revolving fund, the income coming from the charges for drugs sent to the various departments. By such a plan not only the pharmacist but also the department head must carefully watch the purchases. A hospital of 450 beds can successfully function on a budget of $7500 a year, for drugs.

The hospital pharmacist has a very responsible position to fill and can do much to strengthen the position of Pharmacy.

WHO WAS THE AUTHOR OF THE FIRST PHARMACOPŒIA PUBLISHED IN THE UNITED STATES?*

BY C. O. LEE[1] AND F. J. LEBLANC.[2]

The first pharmacopœia to appear in the United States is known as the military pharmacopœia published at Lititz, Pa., in 1778. It has been referred to as a diminutive formulary intended for the use of surgeons in the temporary hospitals during the Revolutionary War.

It is said that only two copies of this original pharmacopœia are in existence. One of these is in the Library of the Surgeon-General's Office at Washington, D. C. A second copy is said to be in the possession of a druggist in Lancaster, Pa.

Most writers upon the subject credit Dr. William Brown as being the author of this first pharmacopœia. Concerning him Wilbert (2) says that little is known about his life and personality. It is recorded that he succeeded Dr. Benjamin Rush as physician-general to the middle department of the Continental Army, July 2, 1777, which position he resigned July 21, 1780 (1).

The *Dictionary of American Biography* states that, "while serving in the Revolutionary Army in 1778, Brown brought out the first pharmacopœia ever published in the United States, a pamphlet of thirty-two pages, written entirely in Latin." It is said to have been based on the Edinburgh Pharmacopœia of the day (6).

The *Index Catalogue* (7) gives the full title of this text and places the name of Brown in brackets [Brown (W)] along with it.

Upon the first page of a reproduced copy of this pharmacopœia there is to be found a note in longhand, addressed to the Junior Physician and Surgeon, General Hospital in which it is stated, among other things, that "the following Pharmacopœia has been compiled." The signature of W. Brown is at the end of the note.

* Section on Historical Pharmacy, A. PH. A., New York meeting, 1937.

[1] Professor of Pharmacy, Purdue University, School of Pharmacy, La Fayette, Ind.

[2] Assistant Professor of Pharmacy, South Dakota State College, Division of Pharmacy, Brookings, South Dakota.

These references might indicate that the authorship of this book should be credited to Dr. Brown. There is nothing, however, so far as we can see, which states it to be a fact. His name was not printed in the text of 1778 as it was in the revision of 1781. The latter appeared a year after his resignation from the service of the Army (6).

DR. JAMES TILTON NAMED AS THE AUTHOR.

In the *Journal of the American Medical Association* for December 26, 1896, there is to be found an article entitled, "Early American Pharmacopœias and Their Authors." It is an editorial of three pages. The reference of Dr. Tilton as the author of the first American Pharmacopœia may be told best by quoting the first thirty-four lines which are as follows:

"The recent International Pharmaceutic Congress at Prague dealt with the history of pharmacopœias but devoted almost no attention to the evolution of pharmacy in the United States. The first attempt at a pharmacopœia in the United States resulted at Lititz, Pa., from the endeavors of Dr. James Tilton of Delaware to secure an official standard as a check on the rapacity of the contractors supplying Washington's army. Dr. Tilton was the first president of the Delaware State society organized in 1789. He was graduated from the University of Pennsylvania in 1771. In 1777 while in charge of the General Military Hospital at Princeton he exposed the "boodleism" and brutality which naturally resulted from laymen having charge of the medical department of Washington's army. Through Dr. Tilton the service was reformed. Relatively inexpensive, readily ventilated, log hospitals took the place of the old mansions previously used. The wounded did not suffer so much from unnecessary travel. Mortality decreased and the health of the convalescent was much improved. Dr. Tilton, like most physicians of the time, took an active part in modeling the statesman-like measures characteristic of the American Revolution. He was several times a member of Congress. During the war of 1812 he was made Surgeon-General U. S. A. He was a man of great executive ability and an excellent sanitarian. He died in 1822 at the age of 77. Among his contributions to medical literature was one advocating the sea-air in cholera infantum.

"The first edition of Dr. Tilton's pharmacopœia appeared in 1778. It was based on the Edinburgh Pharmacopœia and went through a second edition in 1781, Dr. William Brown editing it" (4).

It will be observed that this editorial is rather convincing concerning Dr. Tilton and his relationship to the first American Pharmacopœia. However, we have found but the one article naming him as the author of this book, while there are several which mention the name of Dr. Brown.

In a private communication of recent date the Assistant Librarian of the Army Medical Library, Washington, D. C., wrote, "regarding the Lititz Pharmacopœia, we find that Francis R. Packard in his History of Medicine in the United States is the authority for the statement, to wit:

"At Lititz, another Moravian village in Lancaster County, Penna., a Continental Army hospital was established and maintained from December 1777, until August 1778. . . . . In January, Dr. William Brown, one of the most capable medical officers in the Continental Army and author of the first American Pharmacopœia, was placed in charge of all the Continental Army hospitals in Lititz and its vicinity, and Dr. Francis Allison, Jr., was associated with him."

"The imprimatur of the copy of the Pharmacopœia in this Library bears the place and date of Lititz, March 12, 1778, and so far as known Dr. James Tilton is not associated with the edition of this work."

The few biographical references which we have consulted have much more to say about Dr. Tilton than Dr. Brown. The former served through both the war of the Revolution and the war of 1812.

In 1776 Dr. Tilton was surgeon to a Delaware regiment. 1777–1780 he was in charge of hospitals at Princeton, Trenton and New Windsor, Md. In 1780 he was promoted to senior hospital physician and surgeon and operated a hospital at Williamsburg, Va. At the close of the war he returned to practice at Dover. 1783–1785 he was a member of the Continental Congress. In 1813 he was made physician and surgeon-general of the Army and in 1814 formulated Regulations for the Medical Department to be issued in the general orders. His office was terminated in 1815 by act of congress (8). Tilton is frequently quoted with reference to the hospitals of his time (9).

No attempt is being made in this paper to draw conclusions from the meager evidence which is at hand. We merely wish to call attention to a confusion which should be properly clarified. It is a clear case of the thing that is so apt to happen when people write about matters historical without citing the sources of their information.

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(3) Editorial, JOUR. A. PH. A., 9, 1132 (1920).
(4) Editorial, *J. Am. Med. Assoc.*, 27, 1349 (Dec. 26, 1896).
(5) Private Communication, Army Medical Library (June 25, 1937).
(6) Johnson, A., *Dictionary of American Biography*, 3, 157 (1929).
(7) *Index Catalogue*, Library of the Surgeon's Office, United States Army, Third Ser., Vol. 8, 866 (1929).
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(9) Ashburn, P. M., "A History of the Medical Department of the United States Army" (1929).

INDUSTRIAL RESEARCH LABORATORIES.

REVISION OF BULLETIN 91, NATIONAL RESEARCH COUNCIL.

The increase in the number of research laboratories maintained by industrial concerns in the United States during the last few years has made it seem desirable to issue a new edition of the National Research Council's Bulletin, "Industrial Research Laboratories of the United States," fifth edition.

On March 25th questionnaires were mailed to the 1562 concerns which were included in the last edition of 1933, and to a large number of new concerns which are thought to maintain laboratories.

If the reader of this note is a member of a firm which maintains a laboratory where research looking toward the development and improvement of products is carried on, it is hoped that he will ascertain whether a questionnaire has been received by his company, and if not that he will request one from the Library, National Research Council, 2101 Constitution Avenue, Washington, D. C.

There is no charge for the entry in the bulletin, the only requirement being that the laboratory is undertaking research.

It is desirable to have the information for the bulletin in hand as soon as possible so that the publication may appear within the current year.

PROCEEDINGS OF THE LOCAL BRANCHES

"All papers presented to the Association and Branches shall become the property of the Association with the understanding that they are not to be published in any other publication prior to their publication in those of the Association, except with the consent of the Council." —Part of Chapter VI, Article VI of the By-Laws.

ARTICLE III of Chapter VII reads: "The objects and aims of local branches of this Association shall be the same as set forth in ARTICLE I of the Constitution of this body, *and the acts of local branches shall in no way commit or bind this Association, and can only serve as recommendations to it.* And no local branch shall enact any article of Constitution or By-Law to conflict with the Constitution or By-Laws of this Association."

ARTICLE IV of Chapter VII reads: "Each local branch having not less than 50 dues-paid members of the Association, holding not less than six meetings annually with an attendance of not less than 9 members at each meeting, and the proceedings of which shall have been submitted to the JOURNAL for publication, may elect one representative to the House of Delegates."

Reports of the meeting of the Local Branches shall be mailed to the Editor on the day following the meeting, if possible. Minutes should be typewritten with wide spaces between the lines. Care should be taken to give proper names correctly and manuscript should be signed by the reporter. *Please advise us of changes in Roster and mail reports promptly.*

CITY OF WASHINGTON.

The meeting of the City of Washington Branch, A. PH. A., was held at the AMERICAN INSTITUTE OF PHARMACY on December 13th, President Briggs presiding. The minutes of the previous meeting were read and approved.

L. E. Warren gave an illustrated lecture entitled "Pharmacy and Medicine in Ancient Egypt." The speaker traced the history of Egypt and the use of medicines and drugs by Egyptian priests. A discussion followed the lecture; Mr. Warren answered the questions.

The following resolutions were presented and adopted:

RESOLUTIONS.

WHEREAS during the past two months there have occurred between 90 and 100 fatalities following the use of a medicinal preparation featuring sulfanilamide

AND WHEREAS according to the available data, the toxic effect was attributable not to the sulfanilamide, but to one of the ingredients in the vehicle

AND WHEREAS the toxic substance is a comparatively new chemical in the commercial field, and while not intended primarily for pharmaceutical purposes, its use in the present instance demonstrates that any chemical substance may find its way into medicinal preparations provided it possesses properties that render it attractive as a solvent, vehicle, diluent, bulk producer or what not

AND WHEREAS during the past twenty years a considerable number of new chemicals have been evolved by the manufacturers, and through aggressive salesmanship have been adapted to a variety of commercial uses

AND WHEREAS certain products have been exploited indiscriminately with little or no knowledge of their physiological effects or the industrial hazards attendant on their employment

AND WHEREAS the retail druggist usually has no first-hand knowledge of the composition of the packaged items that he is called upon to sell, and what information he possesses is confined to the declarations on the labels, the claims of the salesman, literature supplied by the producer, such data seldom if ever applying to the vehicles, solvents or diluents

AND WHEREAS when accidents occur it is often the retail druggist selling the article who is confronted with publicity and actions for damage, and even though he may eventually shift the responsibility to the original purveyor, he may suffer unwarranted notoriety and discredit.

Be It Resolved Therefore that in order to obviate this situation as well as to protect the ultimate consumer, this ASSOCIATION recommends the enactment of such legislation as may be necessary to supervise the traffic in chemical substances, in that the physiological effect of the same and the limits of their toxicity may be ascertained, and proper and sufficient labeling provided which will protect the compounder of medicinal products and pharmaceuticals, in the end

that the retailer may not be called upon to dispense dangerous substances of which he has no knowledge.

Be It Further Resolved that these resolutions be transmitted to the parent organization for appropriate action, and to the other branches with the suggestion that similar resolutions be considered.

H. C. Fuller read the program for the next meeting, which was held at the Cosmos Club, on January 17th. He stated that the new officers would be installed.

President Briggs appointed a nominating committee consisting of Messrs. Taylor, Witt, Swann and Fuller; the latter was named chairman. This committee presented the following nominations: *President*, L. E. Warren; *First Vice-President*, I. A. Tennyson; *Second Vice-President*, E. G. Swann; *Third Vice-President*, Miss P. A. Pierson; *Secretary*, K. L. Kelly; *Treasurer*, W. T. McClosky. The nominations were closed and the candidates duly elected, by unanimous vote. They were presented.

V. B. NORELLI, *Secretary*.

JANUARY.

The annual dinner meeting of the Washington Branch of the A. PH. A. was held on January 7th, at the Cosmos Club, with twenty-three present, including ladies. Retiring president Briggs expressed his appreciation to the officers and members of the Branch for their assistance during his term of office and then introduced the new president.

President Warren introduced Abraham T. Schwartz, pharmacist, stationed at the Naval Hospital, who read an instructive paper on "The Duties of a Chief Pharmacist in the United States Navy." This paper presented a critical review of the requirements and the extensive training necessary to fit a man to qualify for this position. In this capacity, his duties are largely administrative, having to do with the handling of personnel, property, and the purchase, examination and distribution of medical supplies. This paper complimented the one presented by Dr. Swann at an earlier meeting; and it was very instructive to those interested in this service.

Dr. Arthur Sievers, who has for many years been connected with the Bureau of Plant Industry of the Department of Agriculture, presented an illustrated paper entitled, "A Brief History of Drug Culture in the United States." This paper is a comprehensive outline of the many efforts in this country to cultivate both foreign and domestic drugs. The yield and strength of the drugs so produced are good but few of these projects have been financially successful due to the relatively small amounts required to meet the present demands, the large amounts of some of these drugs collected in the wild state, and the high cost of labor. This study was undertaken to record the efforts made to meet the problem presented by the decline in domestic production and the interference in importations of certain drugs.

These papers were followed by a bibliographical sketch of the late Dr. Frederick Belding Power, presented by V. K. Chestnut.

Due to the lateness of the hour, the president, upon approval of the meeting, dispensed with the reading of the minutes and introduced one new member, Irving Ness, pharmacist at the Tuberculosis Hospital at Glendale. Chairman Fuller announced that the February meeting, to be held on the 21st, would consist of a joint meeting with the Potomac Trail Club at the Institute Building, the speaker to be Dr. T. S. Githens of Glenolden, Pa.—an illustrated talk on "The Manufacture of Antivenins for Snake Bite."

KENNETH L. KELLY, *Secretary*.

CHICAGO.

The 248th meeting of the Chicago Branch of the AMERICAN PHARMACEUTICAL ASSOCIATION was held Tuesday evening, January 18, 1938, in the Medical College, University of Illinois. The meeting was called to order by President Emig and the report of the Nominating Committee presented, with the following nominees being elected unanimously; for the year 1938–1939: *President*, Herbert M. Emig; *First Vice-President*, Lawrence Templeton; *Second Vice-President*, R. A. G. Linke; *Third Vice-President*, Charles F. Lanwermeyer; *Secretary-Treasurer*, Ralph E. Terry. *Delegate to the House of Delegates*, W. M. Gray. Committee Chairman: Membership, S. W. Morrison; Legislation, J. Harry Lindahl; Practice, Irwin A. Becker; Medical Relations, Dr. Bernard Fantus; Publicity, W. Orlo Knight.

Discussion of the plans for the celebration of the 250th meeting to be held March 15th then followed with announcement of Dr. Ernest Little as the speaker. Several suggestions were made by the group concerning this affair.

President Emig then introduced the speaker of the evening, Mr. Worth Gray of the Technical Service Department of Standard Oil Company of Indiana. Mr. Gray's topic was titled, "The Refining of Petroleum for Medicinal and Pharmaceutical Products."

Mr. Gray stated that until 1914, little advance in the refining of petroleum had been made in the United States with respect to medicinal products. With the outbreak of the World War and disruption of imports of foreign oils and products, the American refiners attempted to transfer the technique used for lubricating oils and greases to medicinal products with little success. Basic types of petroleums essentially similar to Rumanian oils were available but simple distillation and acid treatments were insufficient to produce suitable products. After some experimentation, it was found that ethyl alcohol could be used to wash out the offending petroleum sulfonates and other objectionable substances.

Speaking of "White Oil" or Liquid Petrolatum, Mr. Gray outlined the necessary qualifications which are considered in the choice of the crude oil to be used, such as picking a petroleum which would yield a high quality liquid petrolatum in greatest amount and with the least possible amount of by-products. Since the waste by-products are highly acid mixtures, the disposal problem is very great. They are highly corrosive to metal, low in fuel value and constituted one of the early vexious problems in their disposal. Some of this material is now used as emulsifiers, fat splitters, textile oils for the penetration of dyes, made into greases for pressure lubricants; under proper conditions they can be made into rust inhibitors, and incorporated into printing inks that effect better striking qualities. However the disposal of the excess still remains a problem.

The distillation of the crude oil is carried out in three stages, using a combined steam and vacuum still, the first fraction is used for fuel oil, the second unit is frequently checked for proper specific gravity and viscosity choosing for further refining that fraction which is twice the U. S. P. standards, since additional treatment will result in a loss of fifty per cent of the original values. The residue constitutes petrolatum after bleaching.

Several acid washings are given the high viscosity fraction with mechanical and air agitation to rid the oil of unsaturated hydrocarbons. This takes a period of thirty days or more and results in a loss of about fifty per cent of the oil. On the addition of sodium hydroxide, "mahogany soaps" result removing the residual sulfonates. The oil at this stage is washed with water and then air passed through it to "blow it bright" as it is termed. Decolorization by percolation through fuller's earth to the desired degree of color and final dehydration completes the liquid petrolatum.

The residual third fraction constitutes petrolatum which is bleached by heating with fuller's earth until the desired color results. The oil fraction is removed by diluting with naphtha and cooling to a low temperature which effects a separation. Petrolatum has a definite fibrous crystalline structure dependent upon the original source and the degree to which the refining is carried out.

Mr. Gray discussed the question of storage and packaging of these products, stating that research on this phase had been found to be extremely necessary; in fact equal in amount to that given to distillation and other refining processes.

The production of paraffin was also described with especial mention of the fact that it consists of isomeric compounds of the same carbon content as liquid petrolatum. Since paraffin consists of solids with a definite crystalline structure, their separation from liquid petrolatum is accomplished by chilling and filtering.

An exhibit of the various stages in the refining was shown and after a rising vote of thanks to the speaker, the meeting was adjourned by President Emig.

FEBRUARY.

The 249th meeting of the Chicago Branch of the AMERICAN PHARMACEUTICAL ASSOCIATION was held February 15, 1938. President Emig presided and the following business was transacted: (1) announcement was made of the plans for the March meeting at which the 250th Meeting will be celebrated with a dinner at the Palmer House; (2) the secretary was instructed to prepare and convey a resolution of congratulations on the part of the Branch to Dean W. B. Day on his 67th birthday; (3) announcement was made of the appointment of Ivor Griffith as Dean of Pharmacy at the Philadelphia College of Pharmacy and Sciences.

Following this business session, President Emig introduced the speaker for the evening, Dr. Edgar B. Carter of the Abbott Laboratories whose title was "Ampuls and Their Manufacture and Control." Speaking of Ampuls for intravenous use, since these are examples of the most difficult type to prepare, Dr. Carter outlined his discussion into three units: (1) the chemical; (2) the solvent; (3) the glass ampul itself.

The use of chemicals of reagent grade or of the highest possible purity was pointed out with reasons for the choice of such materials. Along with the use of these chemicals, certain intangible characteristics were discussed. It was pointed out that different sources of supply for the same chemically identical material did not always yield physically equal solutions. The testing of the formula for efficacy, for optimum p_H range, changes under storage conditions, etc., were discussed and the importance of a careful study of all possible points stressed.

The importance of the proper care in use of sterile distilled water was then outlined by Dr. Carter. A short history of the discovery and study of febrile producing protein substances which develop in distilled water which has stood for only a short time was given. Dr. Carter pointed out the manner in which the water becomes contaminated and how necessary it is to prevent the presence of this material in the finished ampul. The use of freshly distilled water and the sterilization of the ampul solutions within a very short time after being made was pointed out as the only method of avoiding this development of pyrogens.

By giving a short history of the production of glass suitable for ampuls, the speaker introduced a very interesting topic. He pointed out the need for a special glass since the purer the water used, the greater was its corrosive effect and that the temperature of sterilization had a great influence on the amount of glass which might go into solution. Changes in p_H of the solution in the ampuls due to solution of the glass and in some cases the production of glass spicules (silicate masses) was discussed, leading into an outline of the tests for glass quality. The sealing of distilled water in ampuls and the heating of these ampuls at 15 lbs. pressure for 20 minutes would determine quickly if the sample of glass was suitable, since unsuitable glass would develop characteristic silicates. The use of Jena Filax glass, the development of American glass formulas of better quality and the present high state of perfection was then outlined.

Finally, the speaker described the methods for determining sterility and how during the period of quarantine, great care is used to prevent possible error. It was pointed out that the N. F. VI for the first time gives definite methods for the sterility tests making them mandatory with all ampul solutions. Inspection techniques through the use of special lighting arrangements was explained. After this questions were asked of Dr. Carter which he answered.

A rising vote of thanks was offered the speaker.

R. E. TERRY, *Secretary.*

MICHIGAN.

The regular meeting of the Michigan Branch of the AMERICAN PHARMACEUTICAL ASSOCIATION was held December 3, 1937. The meeting was preceded by a dinner at Steiner's Restaurant.

A large attendance was in evidence; Ann Arbor as usual was well represented by Dr. H. B. Lewis, director of the College of Pharmacy, University of Michigan, and Professors Charles H. Stocking and J. L. Powers, of the faculty. Also Harvey Whitney, chief pharmacist of University Hospital, E. C. Watts his assistant, and Jerry C. Totzka, director of drugs and drug stores.

The meeting was called to order by President Earl Soop at 7:15 P.M. Owing to the limited time, minutes of the previous meeting were omitted. Dean R. T. Lakey reported on the activities of the Program Committee. President Soop named a membership committee in accordance with the motion of R. W. Klein to enlarge activities of the branch and its membership.

Members of the committee appointed are: Prof. C. H. Stocking, University of Michigan; Ralph J. Mills, Wayne University; J. L. Dorian, Detroit Institute of Technology; E. C. Watts, Hospital Pharmacy; Earl Soop, Students: Walter M. Chase, Industrial Pharmacy; Maison G. de Navarre, Cosmeticians; James T. Liddle, East Side; Joseph J. Burniac, West Side; R. W. Klein, North End; Leonard A. Seltzer, Downtown; out-of-state members to be added later.

John H. Webster opened a general discussion regarding the status of the assistant pharmacist after January 1938, when the new pharmacy law goes into effect. Mr. Totzka and the

members of the Board of Pharmacy were agreed that the status by law of the assistant would be no different than it has been; that is, after twenty-five years' experience as an assistant registered pharmacist he would receive a certificate as registered pharmacist, as provided in the existing law. Messrs. Stocking, Seltzer, Lakey, Webster, McCabe and Whitney took part in the discussion.

At 7:45 the meeting adjourned to the auditorium of the College of Pharmacy and Medicine of Wayne University to join with the University and the Detroit Retail Druggists' Association in a program presented by Dr. A. D. Emmert of Parke, Davis & Co. and member of the United States Pharmacopœial Committee on Vitamins and an authority in this field.

Dr. Emmert gave a most timely talk on vitamins in health and disease. The lecture was illustrated with lantern slides and demonstrations on living animals showing the effects of vitamin therapy upon them. This proved most interesting to the many pharmacists and ladies in attendance, which numbered about 250. The hearers were left better equipped with knowledge on vitamins, thus enabling them to present these products more intelligently to the physician and his patients.

BERNARD A. BIALK, *Secretary.*

JANUARY.

The January meeting of the Michigan Branch of the AMERICAN PHARMACEUTICAL ASSOCIATION was held January 7th.

The meeting was preceded by a sizzling dinner. The two Detroit Colleges of Pharmacy were well represented by members of the faculty. Dean Lakey and Mr. Mills represented Wayne University, College of Pharmacy, and Dean Stout of Detroit Institute of Technology and Professors Dorion, Warner and Emmert. The absence of Ann Arbor representatives and the University of Michigan broke a long chain of record attendances by this loyal group. President Earl Soop, Wayne University, presided at the meeting.

It was decided to again give over a meeting to the students of the Colleges of Pharmacy. Invitations will be extended to the recognized colleges of pharmacy in Michigan to participate in this annual Student Night program.

After congratulating the F. E. R. A. Committee for the splendid results accomplished during 1937 and for harmoniously working with the Wayne County Medical Society, President Soop re-appointed the Committee composed of Leonard A. Seltzer, *Chairman*, Bernard A. Bialk, Samuel Bornstein, W. A. Frohme, T. T. Matthews and Joseph F. Tandy.

The meeting was adjourned at 8:00 P.M. to the auditorium of the College of Pharmacy and Medicine of Wayne University to attend the lecture arranged by the Detroit Retail Druggists' Association and the College of Pharmacy of Wayne University.

"Endocrinology and the Pharmacist," an illustrated talk, delivered by Dr. D. H. Kitchen, endocrinologist of Parke, Davis & Company, an outstanding authority in this vast field which is playing such an important part in Medicine to-day, follows.

"The first hormone isolated in its pure crystalline form was Adrenalin from the adrenal medulla by Takamine in 1901. This discovery gave added impetus to the field of endocrinology and most of our present-day knowledge dates from that time, particularly the last ten years.

"The physician at the present time has at his command a larger number of hormone preparations which are available in a high state of purity and concentration. It remains only for our knowledge of diagnosis to advance to an equal level for results with organotherapy to be even more striking.

"The pharmacist to-day has an important place in this rapid advancement. As further strides are made even greater demands will be made upon you to supply active hormones on prescription to the laity. This subject will be discussed in detail.

"The average busy physician does not have the time to keep abreast of all phases of this rapidly advancing field. How many times every day is the pharmacist asked for rather definite information covering endocrinology or organotherapy? Obviously the pharmacist has a most important rôle, and for this reason he should continue to familiarize himself with the latest developments in the field.

"The pharmacist should above all be acquainted with the purity of hormones and the methods used in standardization of these all-important weapons. He should familiarize himself

with recommendations regarding dosage, and with factors such as stability, available packages and the many other things discussed in this lecture."

Illustrations in the form of lantern slides demonstrated in general the present status of glandular physiology and therapy.

The meeting, like the previous ones, was well attended by both men and women interested in the advancement of pharmacy. They were well rewarded, as Dr. Kitchen's talk was most interesting and instructive and unusually well presented. This lecture was the third of a group of "Continuation-Study" programs arranged by Wayne University and the D. R. D. A. and they are doing much to impart knowledge to pharmacists, to enable them to serve the public health and the physician.

BERNARD A. BIALK, *Secretary.*

FEBRUARY.

The February meeting of the Michigan Branch of the AMERICAN PHARMACEUTICAL ASSOCIATION was held in the Wayne County Medical Society Building, February 15, 1938. It was preceded by a dinner. President Earl Soop called the meeting to order, the minutes of the previous meeting were read and approved.

Prof. C. C. Glover, in behalf of Dr. H. B. Lewis and the faculty of the University of Michigan, extended to the Michigan Branch an invitation to hold its May meeting in Ann Arbor in conjunction with the Pharmaceutical Conference sponsored by the University of Michigan, College of Pharmacy, May 18, 1938.

The principal speaker will be Dr. Robert L. Swain, president, American Boards of Pharmacy and secretary of the Maryland State Board of Pharmacy. Other speakers will include Dean Roland T. Lakey of Wayne University; Otis F. Cook, Secretary, Michigan State Pharmaceutical Association; and R. L. McCabe, member of Michigan State Board of Pharmacy.

President Soop read an invitation from the Chicago Branch, A. PH. A. to the members of the Michigan Branch to attend the 250th meeting of the Chicago group on March 15, 1938.

The president then introduced J. Edward Richardson, former president of the D. R. D. A. and Michigan Board of Pharmacy, who introduced the speaker of the evening, Treasurer Albert E. Cobo, of the City of Detroit. He was loaned by Industry to the City when they found themselves in need in financial difficulties.

It seems all that Mr. Cobo did was to apply business sense and principles. He illustrated his talk with many startling figures taken from the records of the city treasury; $22,000,000 was written off in five years; the first time in history that the City debt has been reduced. This was accomplished while taxes were lowered $100,000,000 in the past four years.

A $76,000,000 budget in five years reduced to $59,000,000 and besides the City employees received 5% more salary than in 1929—the saving was not taken out of the employees' salary.

Selling of back taxes was stopped, as no revenue was produced by outside buyers who were interested only in receiving from the unfortunate individual who was unable to pay the normal tax. Mr. Cobo installed the part-payment plan and the City has collected $7,000,000 in interest alone on back taxes.

In 1934 the City budget was $8,000,000 out of balance, this was corrected by curtailing expenses and increasing the revenue. He said the City finds itself in the same position to-day, unless the budget is balanced—an increase in revenue is necessary.

WELFARE PROBLEM.

The welfare problem to-day is estimated to cost the City of Detroit $7,000,000 and the State $2,000,000 and the peak has not been reached according to Mr. Cobo. He said $15,000 probably would be added making it necessary to raise $2,500,000 to finance.

He stated it has been his endeavor to tax within the reasonable power of people to pay. The program for property tax in this City is the finest in the country, and by eliminating the tax buyer, milking of property and profiteering has been eliminated and the City Treasury was benefited.

To illustrate his point he said $13,000,000 was paid by apartments alone when the City Treasurer began action; 15,000 apartments owed back taxes; this number was brought down to 588, unpaid after the first letter from the City Treasurer. Only 190 appeared before the Council

for reduction in taxes; 486,000 parcels of property remain on the books for unpaid taxes, many of these are vacant lots.

He said the local government employed 36,000 people, more than the population of many cities in the state. The magnitude of the City Treasurer's job was illustrated by the 976,000 new accounts set up by Mr. Cobo in the five years he has served the City.

He covered the field so thoroughly that not much was left for discussion. Joseph Kearney of the Assessor's Office asked how Detroit compared with cities of like problems. Mr. Cobo said Detroit was fourth in the amount given the taxpayer for his dollar and complimented the Assessor's Office for its aid in making this possible.

L. A. Seltzer complimented the speaker and in thanks offered a rising vote which was enthusiastically given by a good attendance.

The meeting adjourned at 9:30 P.M., every one satisfied the city treasury was in safe hands.

The March meeting of the Michigan Branch, A. PH. A. will be held in Wayne County Medical Building, Tuesday, March 22, 1938. Dinner will be at 6:30 P.M. and the program will follow immediately. Non-members, students and ladies are cordially invited and incur no obligation. An interesting "Prescription Clinic" is planned by the program committee.

BERNARD A. BIALK, *Secretary.*

NEW YORK.

The monthly meeting of the New York Branch of the AMERICAN PHARMACEUTICAL ASSOCIATION was held on Monday evening, January 10, 1938, at Columbia University, College of Pharmacy, President Schaefer presiding. The minutes of the previous meeting were read and approved.

The treasurer's report showed a balance of $302.12.

The officers were elected—see January JOURNAL, page 59.

President Schaefer introduced the officers to the meeting; expressed his thanks to Dr. Hugo Schaefer for his work in making the 1937 convention such a success, to Mr. Mason of the Program Committee and to Secretary Givens, and then turned the chair over to President Canis.

Chairman R. S. Lehman reported for the Committee on Education and Legislation.

National Legislation.—The President's message to Congress on the state of the union, was received with more favor than the public utterances of the representatives of the administration immediately preceding it. The market reacted with an upward trend.

Congress will be called upon to enact a wage and hour bill; a bill reorganizing the Executive Departments; revising the revenue law, particularly the capital gains tax and undistributed gains tax provisions; a bill strengthening the anti-trust laws.

Minimum Price Contracts Legal.—The Federal Trade Commission issued an order dismissing complaints against Bristol-Meyers Company and Yardley's in which they were charged with retail price maintainence in violation of the Clayton Act.

President Canis appointed Mr. David Mason as *Chairman* of the Program Committee, and the following Delegates and Alternates to the New York Pharmaceutical Council:

Delegates.	Alternates.
Otto F. A. Canis	James H. Kidder
Frederick C. A. Schaefer	John J. Corcoran
Jacob Seley	A. White
Horace T. F. Givens	Charles Heimerzheim
L. C. Jayne	George Decker
Peter C. Anselmo	Jack Feldman

Dr. Herman Goodman presided as chairman of the Scientific Section on a "Symposium on Color."

Dr. Goodman gave some "Introductory and Historical Remarks on Physiology and Pharmacology."

Color in Food, Cosmetics and Drugs: Introductory and Historical Remarks on Physiology and Pharmacology.*

BY HERMAN GOODMAN.

The appeal of color has been universal through the ages. The search for color has lead man into many byways, off into unknown lands and across trackless oceans. Columbus sought a short route to the color storehouses of the Indies because of the tribute exacted by the roving robber bands of the old land routes.

Natural vegetable, animal and mineral colors were relatively scarce and costly as the name Royal Purple obviously implies. Yet, an English schoolboy, home on his Easter vaction working in a kitchen laboratory on problems which have remained unsolved 100 years later, discovered the first of the coal-tar colors, mauve or Royal Purple. The lowly tar barrel has been dissected and forced to disclose many of its secret quotients of color and odor. Since 1856 coal-tar colors have practically displaced the natural products which once alone supplied the world with color.

The coal-tar barrel first tapped by the boy Perkin, also became the source of experimentation of another youth in his teens. Paul Ehrlich began his studies and experiments with coal-tar preparations. He distinguished the members of the white blood-cell series by their dyeing reactions. He discovered the acid-fast nature of the tubercle bacillus recently discovered by Koch. Ehrlich acquired tuberculosis from these studies. He produced vital staining. He named the gonococcus. He advanced the theory of the immunity reaction known as the side-chain theory. This was the source of Wasserman's efforts which led to the serological reaction or blood test for syphilia. Ehrlich evaluated the diphtheria antitoxin so it could be standardized and injected safely. He studied the oxygen requirements of living organisms. Ehrlich failed in his attempts to learn the basic nature of cancer.

But starting with the base dye substance, atoxyl, and proceeding through hundreds of chemical modifications, Ehrlich with the 606th experiment devised a dye which has been a boon to suffering man. Syphilis and frambesia have been reduced because of the dream of Ehrlich. Truth to tell, the idea of a one-dose cure which Ehrlich felt was possible has not been attained, but 606 or 914 and their modifications and substitutes on the Ehrlich formula are not dreams.

Other healing products have been taken from the coal-tar colors, as the group of flavin antiseptics and the mercury chrome carriers. There are innumerable anesthetics and soothing remedies from coal tar, too.

On the other side of the ledger, there are hosts of explosives, poison gases and other products of the tar barrel which upset national economy and lead to strife.

Cancer and cancer-like reactions to the experimental application of coal-tar quotients have been reported. Who can foretell when some student of the color art will d sclose some dye which will end the scourge of the human race by revealing the care or prevention of cancer.

The dyes which have been presented to us for the alleviation of disease, for the decoration with color and odor of our food, cosmetics and drugs are not undiluted blessings. Some few persons react differently than the great majority. Altered reactivity or allergy has been the subject of much study and concern by associations as this one and the Board of Standards of the Toilet Goods Association, for example. Allergy does not restrain us from the application of coal tars in helpful addition to the beauty of life, to the restoration of healthful life, or possibly, life itself.

Although products already available from the tar barrel are too numerous to name, it is but a beginning. To-morrow and the day after, coal tar will still remain a source of pleasure and health. We must pay our respects to the founders—Perkin and Erhlich. We anticipate new heroes in the art and science who will carry on their work. Meantime, all people may enjoy the fruits which were beyond imagination a few decades ago.

Prof. Abraham Taub presented the subject of "Color Standardization."

He discussed the need for color standardization, the present lack of uniformity in color names and the lack of standards for colors used in cosmetics, in contrast to the standardized certified colors used in food and drug products. He enumerated the available color standards for transparent and opaque substances, the types of colorimeters and their advantages and short-

* Summary of Paper delivered before the New York Branch of the American Pharmaceutical Association, January 10, 1938, at Columbia University, College of Pharmacy, 115 West 68th Street, N. Y. C.

comings, and concluded with a description and demonstration of the spectrophotometer, as the only instrument which yields a scientific description of color. He made a plea for the use of colors of non-secret composition and expressed the hope that the industry and pharmaceutical profession would set up their own standards of uniformity and purity rather than await bureaucratic regulations.

Albert Suess discussed "Practical Methods of Color Addition to Foods and Drugs."

Kenneth W. Ebert discussed some difficulties in the manufacture of new certified colors. The talks were accompanied by color exhibits and instruments.

Several men prominent in the field took part in the discussion.

A rising vote of thanks was accorded the speakers.

FOOD, DRUG AND COSMETIC COLOR SYMPOSIUM.

The New York Branch of the AMERICAN PHARMACEUTICAL ASSOCIATION for its January meeting, arranged a symposium on color in food, drugs and cosmetics for January 10th at the College of Pharmacy, Columbia University. The scientific section, to which the public is invited, begins at 9:00 P.M.

Following the custom of offering many aspects of the same problem by several speakers, the committee has invited a number of specialists in this field. A prominent dermatologist, Dr. Herman Goodman, of the Brooklyn College of Pharmacy, L. I. University, presided as chairman. The subject of color standardization was presented by Abraham Taub, Associate Professor of Pharmaceutical Chemistry, Columbia University, College of Pharmacy. Albert Suess, consulting color chemist, formerly of Leipzig University, discussed practical methods of color addition to foods and drugs. Mr. Thomasat, chemist for the Ansbacher-Siegle Corp., reviewed the chemistry of color. The talks were accompanied by color exhibits and instruments.

The symposium closed with a critique by Mr. Kenneth W. Ebert of the Interstate Color Co., and by several consulting chemists of distinction. HORACE T. F. GIVENS, *Secretary.*

NORTHERN NEW JERSEY.

The Northern New Jersey Branch of the AMERICAN PHARMACEUTICAL ASSOCIATION met at Rutgers College of Pharmacy, January 17, 1938. Doctor Marquier demonstrated a method for quickly preparing Compound Tincture of Cardamom that from the standpoint of elegance and economy has much to recommend it. Oil of Cardamom Seed 1.0 cc., Oil of Cinnamon 0.5 cc., Oil of Caraway 0.6 cc. Tincture of Cudbear Compound 15.0 cc., Alcohol 475.0 cc., Glycerin 50.0 cc., Distilled Water 475.0 cc. Dissolve the oils in the alcohol, add the glycerin, the distilled water, and lastly the tincture of cudbear compound.

Dr. Ralph W. Clark, of Merck & Co., read a paper in which he emphasized the relation of the pharmacist to public health; the value of the prescription to the physician; the economic status of the prescription to the pharmacist; the salesmanship and showmanship potentialities of the prescription; the advertising value of the visible prescription case, and the eagerness of the prescription chemical manufacturers as well as the pharmaceutical establishments to coöperate in building better prescription business. C. L. COX, *Secretary.*

NORTHERN OHIO.

The regular monthly meeting of the Northern Ohio Branch of the AMERICAN PHARMACEUTICAL ASSOCIATION was held at the Faculty Club of Western Reserve University on Friday, February 11, 1938. This was a dinner meeting and after some routine business matters were disposed of, the guest speaker, Dr. Gerald S. Shibley, 10515 Medical Building, Carnegie Ave., Cleveland, was introduced.

Doctor Shibley talked on "Pneumonia." Incidence, bacteriologic types, symptoms, complications and therapy were discussed. The speaker gave a considerable portion of his time to the methods employed for "typing" the disease and emphasized the point that this must be done very early in the course of its onset. Statistics were given showing the results of antipneumococcus serum treatment on the various type organisms. Serum treatment is the most successful

method for treating the disease. Other specific therapy has been rather disappointing. Oxygen inhalation by the latest improved methods may be used to advantage to carry the patient over the crisis.

N. T. CHAMBERLIN, *Secretary.*

NORTHWESTERN.

The Northwestern Branch (AMERICAN PHARMACEUTICAL ASSOCIATION) held three meetings on three successive days in the auditorium of the College of Pharmacy of the University of Minnesota at which the following distinguished lecturers addressed the membership of the Branch and the student body of the College.

Monday, January 31st, "Therapeutic Agents Used in the Treatment of Anemia." Dr. Frank J. Heck, Assistant Professor of Medicine, Mayo Clinic, Rochester, Minn.

Tuesday, February 1st, "Local Anesthetics." Dr. F. F. Blicke, Professor of Pharmaceutical Chemistry, College of Pharmacy, University of Michigan, Ann Arbor, Mich.

Wednesday, Feb. 2nd, "Sex-Hormone Preparations." Dr. J. D. Ralston, Parke, Davis and Co., Detroit, Michigan.

These lecturers were members of the faculty of the Pharmaceutical Institute of the University of Minnesota which was in session at the time. The officers of the Branch were fortunate in securing these men for this series of lectures.

CHAS. V. NETZ, *Secretary-Treas.*

PITTSBURGH GRADUATE CHAPTER—KAPPA PSI.

The monthly meeting and dinner of the Pittsburgh Graduate Chapter of Kappa Psi Pharmaceutical Fraternity was held January 19th. The Beta Kappa Chapter was the guest of the Graduate Chapter.

There were shorts talks given by the members. Motion pictures was the added attraction for the evening.

F. J. STEELE, *Historian.*

PHARMACEUTICAL SYMPOSIUM.

The Medical College of Virginia, Richmond, Virginia, presented a Pharmaceutical Symposium of the Centennial Celebration, February 16th, in the Richmond Academy of Medicine Auditorium. The announcement is signed by President W. T. Sanger, Dean W. F. Rudd and the Chairman of the Program Committee, T. D. Rowe.

The Program was as follows: "The Pharmacist and Public Health," Dr. L. C. Riggin, State Health Commissioner of Virginia; "The Practice of Professional Pharmacy," Mr. Eldon Roberts, Jr., Retail Pharmacist; "The Pharmacist and The Physician," Dr. J. Leon Lascoff, President-Elect of the AMERICAN PHARMACEUTICAL ASSOCIATION.

President-Elect J. Leon Lascoff, AMERICAN PHARMACEUTICAL ASSOCIATION, and Hon. President, New York State Pharmaceutical Association showing Dean Wortley F. Rudd and T. D. Rowe, Pharmacy School, Medical College of Virginia, his display of correct and incorrect medical prescriptions on display in the auditorium of the Richmond Academy of Medicine where Virginia's Pharmaceutical Symposium celebrating the Medical College Centennial, was held in February. (Left to right) Dean Rudd, Dr. Lascoff and Mr. Rowe.

Photo State Chamber *of Commerce.*

HAROLD M. FARKAS, *Science News Director.*

ASSOCIATION BUSINESS

AD INTERIM BUSINESS OF THE COUNCIL OF THE AMERICAN PHARMACEUTICAL ASSOCIATION, 1937–1938.

Office of the Secretary, 2215 Constitution Ave., Washington, D. C.

LETTER NO. 4.

December 30, 1937.

26. Local Secretary for 1937–1938. Motion No. 4 (Council Letter No. 3, page 71) has been carried and Dr. Rogers has been advised of his election.

27. Time and Headquarters for the 1938 Meeting. Motion No. 5 (Council Letter No. 3, page 71) has been carried and Local Secretary Rogers has been advised that the week of August 22nd to 27th has been approved as the time and the Hotel Nicollet as the headquarters for the Minneapolis meeting.

28. Election of Members. Motion No. 6 (Council Letter No. 3, page 72) has been carried and applicants for membership numbered 74 to 150 are declared elected.

29. Budget for 1938. Chairman Swain of the Committee on Finance submits, in accordance with Article II of the By-Laws of the Council, the following report on the appropriations and expenditures for 1937 with a proposed budget of receipts and appropriations for 1938 which were prepared by the secretary and approved by the Committee.

Receipts for 1937.—The receipts to December 1st are compared to the receipts for the same period in 1936 and to the estimates for 1937, as follows:

	12/1/37.	12/1/36.	Estimate for Year.
Dues	$ 9,445.65	$ 7,999.56	$14,000.00
JOURNAL and ABSTRACTS	7,281.72	7,273.14	9,500.00
Recipe Book	2,726.23	154.18	6,000.00
YEAR BOOK and Miscellaneous	147.27	104.27	1,500.00
National Formulary	20,776.42	101,208.56	17,500.00

The bills for dues for 1938 were mailed December 1st, and the receipts during the month indicate that the dues will exceed the estimate.

Disbursements for 1937.—To December 1st, only one appropriation for General Expenses had been exceeded, the disbursements for Printing, Postage and Stationery amounted to $760.86 against $700.00 appropriated. The disbursements for General Expenses totaled $18,358.81 to December 1st, against $25,330.00 appropriated for the year.

Of the appropriations for Open Accounts, none have been exceeded to December 1st, and the disbursements for this period totaled $18,586.35 against $23,550 appropriated for the year. The disbursements for the JOURNAL and ABSTRACTS totaled $16,580.21 to December 1st, against $17,000.00 appropriated.

Receipts for 1938.—The following is the best estimate of receipts than can be suggested at this time:

Dues	$15,500.00	
JOURNAL and ABSTRACTS	10,500.00	
National Formulary (5000) copies	17,950.00	
Recipe Book (1000 copies)	4,308.00	
YEAR BOOK and Miscellaneous	1,200.00	$49,458.00

APPROPRIATIONS FOR 1938.

For General Expenses.

No. 1	Salaries	$12,900.00
No. 2	Maintenance of Building	4,200.00
No. 3	Telegraph and Telephone	300.00
No. 4	Clerical Expenses	1,300.00

No. 5	Printing, Postage and Stationery		800.00	
No. 6	Office Supplies		250.00	
No. 7	Traveling Expenses		750.00	
No. 8	Premium on Bonds		50.00	
No. 9	Auditing		75.00	
No. 10	Certificates		25.00	
No. 11	Miscellaneous		150.00	
No. 12	Scientific Section		25.00	
No. 13	Section on Education and Legislation		25.00	
No. 14	Section on Practical Pharmacy & Dispensing and Sub-section on Hospital Pharmacy		50.00	
No. 15	Section on Pharmaceutical Economics		25.00	
No. 16	Section on Historical Pharmacy		25.00	
No. 17	Committee on Proprietary Medicines		50.00	
No. 18	Committee on Local and Student Branches		50.00	
No. 19	Committee on Membership		800.00	
No. 20	Committee on Pharmacy Laws		50.00	
No. 21	Committee on Syllabus		50.00	
No. 22	Committee on Pharmacy Week		250.00	
No. 23	Committee on Emblem		50.00	
No. 24	Committee on Dental Pharmacy		50.00	
No. 25	Inter-Society Color Council		25.00	
No. 26	International Pharmaceutical Federation		120.00	
No. 27	Metric Association		10.00	
No. 28	American Council on Pharmaceutical Education		200.00	
No. 29	Exhibits		350.00	$23,005.00

For Open Accounts.

No. 30	JOURNAL and ABSTRACTS			
	(*a*) Publication	$9200.00		
	(*b*) Clerical Expenses	1300.00		
	(*c*) Postage and Stationery	300.00		
	(*d*) Freight and Miscellaneous	200.00		
	(*e*) Abstracts	5000.00	$16,000.00	
No. 31	NATIONAL FORMULARY			
	(*a*) Clerical	1100.00		
	(*b*) Bulletins and Letters	900.00		
	(*c*) Office Supplies	300.00		
	(*d*) Chairman's Travel Expenses	400.00		
	(*e*) Research (A. PH. A. Laboratory)	3000.00		
	(*f*) Printing	3100.00	$ 8,800.00	
No. 32	RECIPE BOOK			
	(*a*) Revision	300.00		
	(*b*) Binding	600.00	$ 900.00	25,700.00
	Total Appropriations for 1938			$48,705.00

The appropriation for Salaries carries $1200 for an accountant to assist the secretary in accordance with Item No. 14, Council Letter No. 1, and the appropriations for the National Formulary are arranged to take care of revision expenses and the contribution to the A. PH. A. Laboratory as recommended by Chairman Gathercoal.

It will be necessary to later make additions to the budget to cover the new activities which are now being arranged for.

(*Motion No. 7*) It is moved by Swain that $100.00 be added to the appropriation for Printing, Postage and Stationery for 1937; and that the proposed budget for 1938 be approved as submitted. With the approval of the chairman of the Council, a vote is called for at this time but will be considered as tentative if there is objection.

30. Selection of Auditor. The Committee on Finance recommends the employment of W. A. Johnson, Baltimore, Md., to audit the accounts of the ASSOCIATION for 1937, in accordance with Article VIII of Chapter IV of the By-Laws. Mr. Johnson had audited the accounts since 1922 and the appropriation for the audit has been $75.00 for each year.

(*Motion No. 8*) It is moved by Swain that W. A. Johnson, Baltimore, Md., be selected to audit the accounts of the ASSOCIATION for 1937 at a cost of $75.00.

31. Honoraria to Members of the Committee on National Formulary. The Committee on Finance has given careful consideration to this matter as referred to it by the Council and after conferring with the chairman of the Committee on National Formulary, recommends that the amounts given on the list attached to this letter be paid to the persons named thereon as a recognition of their services as members of this Committee. It is further recommended that in forwarding the honoraria an appropriate letter be addressed by the secretary to those named, in which the deep appreciation of the ASSOCIATION for the valuable services rendered by the members of the Committee will be expressed, and that a certificate similar to that issued to the members of the preceding committee be prepared and forwarded as promptly as is possible.

(*Motion No. 9*) It is moved by Swain that honoraria as recommended be paid to the members of the Committee on National Formulary, that a letter expressing the appreciation of the ASSOCIATION be sent as recommended and that a certificate as recommended be prepared and forwarded as promptly as possible.

32. Applicants for Membership. The following applications, properly endorsed and accompanied with the first year's dues, have been received:

No. 151, F. Milton Cook, 203 University Ave., Oxford, Miss.; No. 152, B. V. Yelverton, Box 34, University, Miss.; No. 153, Louis F. Bocchicchio, 7105 Monticello St., Pittsburgh, Pa.; No. 154, Richard Parson, 558 Ridge Ave., New Kensington, Pa.; No. 155, A. Edward Collins, 436 Marion St., Pittsburgh, Pa.; No. 156, Alvin Luhr, R.F.D. No. 1, Clayton, Wash.; No. 157, Norvin Lewis, Box 877, College Sta., Pullman, Wash.; No. 158, Curtis H. Waldon, 903 Washington Ave., S.E., Minneapolis, Minn.; No. 159, Herman Leven, 1923 St. Ives, Pittsburgh, Pa.; No. 160, Alan Norris, c/o Unity Chemical Co., 67 Carlton St., Toronto, Canada; No. 161, Kenneth Redman, c/o N. Dak. Agri. College, Fargo, N. Dak.; No. 162, William Ralph Jackson, Merck & Co., Inc., Rahway, N. J.; No. 163, Sister Mary Alexius, 307 S. Euclid Ave., St. Louis, Mo.; No. 164, Charles Iskander AbouChaar, American Univ. of Beirut, Beirut, Lebanon; No. 165, Carl A. Swisher, 2035 Adelbert Rd., Cleveland, Ohio; No. 166, Joseph Harry Beckerman, 456 Crescent St., Brooklyn, N. Y.; No. 167, Sophia Robart, 45 Newbury St., Boston, Mass.

(*Motion No. 10*) Vote on applications for membership in the ASSOCIATION.

E. F. KELLY, *Secretary.*

LETTER NO. 5.

To the Members of the Council: January 15, 1938.

33. Budget for the A. Ph. A. Laboratory for 1938. The following report with recommendations, has been received from the Committee on Laboratory through Chairman Gathercoal:

INTRODUCTORY.

Before presenting the budget, the Committee would recall to the attention of the Council certain items in the previous reports of the Committee.

First.—In the Committee meeting of July 1, 1937, the scope of the laboratory was defined as follows: "To investigate for the purpose of standardization, the physical, chemical and biological properties of substances and preparations used in the diagnosis and treatment of disease."

Second.—In the Committee meeting of August 14, 1937, after extensive discussion, Dr. Krantz and Chairman Gathercoal presented the following statement: "The *purpose* of the Laboratory was well set forth in the words of Dr. Rosin in paragraph 3, page 71, Letter No. 3 (see paragraph above), but the *scope* needs better definition. Therefore, the following outline is offered as a more complete definition of the scope of the laboratory." (The outline is not repeated here in full):

A—Determination of Physical Constants
B—Chemical Determinations
C—Pharmaceutical Determinations
D—Pharmacognostical Determinations

E—Bacteriological Determinations
F—Pharmacological Determinations
G—Photography

A detailed classification under each item and the apparatus needed for all of this work is indicated in the report. Furthermore, the need for specific rooms such as constant temperature room, dark room, bacteriology room, etc., is pointed out.

The Committee has fully endorsed the scope of the Laboratory as set forth above and has endeavored to provide the necessary rooms, even though some of them be on a rather small scale. Therefore, the blueprints of the ground plan show the following rooms:

Chemical Laboratory
Physico-Chemical Laboratory
(Constant Temperature Room)
Pharmacological and Pharmacognostical Laboratory
Bacteriology Room
Dark Room
Director's Office
Secretary's Office
Storage Room
Shop

Third.—In the recommendations of the Committee presented to the Council at the New York meeting of the A. PH. A., which recommendations were approved by the Council, the sum of $25,000, or such portion thereof as may be necessary, is appropriated from the special and general funds available for this purpose for the period ending December 31, 1938, and for the purpose of carrying out these recommendations.

The Committee on Laboratory has held two meetings since the New York meeting and has carried on its work through circulars and personal conferences.

The services of an architect-engineer have been engaged for preparing the drawings and specifications for the necessary partitions and changes in the plumbing, electrical work, etc., and in arranging for the necessary legal permits.

Conferences have been held with representatives of interested firms in regard to the laboratory furniture. Bids have been submitted by these firms. Conferences have also been held with certain firms dealing in office furniture.

As a result of these activities certain items of office furniture have been tentatively ordered; the Committee has approved of the bid of the Kewaunee Manufacturing Company for the laboratory furniture and arrangements are being made for the preparation of the rooms.

In the period of September 1 to December 31, 1937, $799.26 of the laboratory appropriation has been expended ($278.39 for apparatus, $280.87 for traveling expenses and $240.00 for salaries for two men in the N. F. Laboratory for the month of December) and this amount is included in the following itemized budget as recommended by the Committee:

BUDGET.

Permanent Investment.—The Laboratory Committee has understood that $10,000 was to be available for the furnishing and equipping of the laboratory. The Committee early considered that about $5000 should be spent for laboratory and office furniture, about $4000 for permanent apparatus and about $1000 for the preparation of the rooms.

A general bid on the preparation of the rooms in accordance with the first plans submitted by the Committee was $8000. After the architect had been engaged and a careful study made of the present plumbing, electrical wiring, etc., further blueprints were prepared and the general bid came down to $6000. Since then further studies have resulted in yet another floor plan and it is expected that the rooms can be prepared now for not more than $4000. However, this is a large sum to take out from $10,000 set aside for the furnishing and equipping of the laboratory. The cost of this type of work in Washington is very high and the local requirements very rigid. Certain facilities that the laboratory should have are being deferred on account of the cost, but the basic requirements are being supplied.

The early bids received indicated that the twenty-one items of laboratory furniture needed could be had in the standard type (paneled and overhanging doors and drawers) for $5500. However, this laboratory, which will be not only a workshop but also a show place, should be equipped not only with well-made furniture, but that which is modern and good appearing. Bids

on the ply-roll type of construction were about 10% higher than the standard construction. The Committee is recommending to the Council the purchase of the Kewaunee Company flush front, ply-roll construction with karcite sinks, kemstone tops, black plastic drawer pulls and door knobs, oxidized red copper service equipment, with the woodwork finished in black walnut and acid and alcohol-proof synthetic varnish. This furniture includes two double chemical tables; seven single, wall chemical tables (all equipped with water, drain, gas, air and electrical connections); four tables without service connections; four cabinets with glass doors, drawers and cupboards; one titration table; and three fume hoods. The bid price for this furniture delivered and installed is $6232.28.

The office furniture consists of a desk, library table and three chairs in the director's office; a desk, three chairs, six filing cabinets and two sets of book shelves in the secretary's office; four desks and six chairs in the laboratories, six adjustable stools, six steel coat lockers, wastebaskets, etc. The early bids on this furniture ran about $650.00 to $1000. However, it has been possible to purchase in Philadelphia a high grade of black walnut furniture including the six desks, table, six desk chairs and the six side chairs for $294.00 delivered at Washington. It is believed that the six stools, the six lockers, six filing cabinets, the book shelves and wastebaskets can be purchased for the remainder of $500.00.

If $4000 is spent for the preparation of the rooms, $6250 for the furniture and $500.00 for the office furniture, nothing will be left out of the $10,000 for the permanent apparatus. However, provision has been made for the purchase of a considerable number of pieces of such apparatus, to meet immediate requirements, and additions are expected as explained later in this report.

Maintenance Expenses.—It was understood by the Laboratory Committee that the annual maintenance expense was to be kept within $15,000.

The Laboratory Account is to assume the expense of the N. F. Laboratory at Chicago until its transfer to Washington. It is expected that this transfer will take place about June 1st, and therefore the salary budget is divided into two parts: January 1st to May 31st and June 1st to December 31st.

Three men are engaged in the Laboratory at Chicago, though one of these on half time is paid from the A. PH. A. research fund grant to the University of Illinois. The other two are now receiving $120.00 per month. The fourth, engaged in the color research at the Bureau of Standards at Washington receives $100.00 per month. The salaries for the first five months, therefore, will be $1700. The honorarium for six months due Professor Gathercoal on March 1st is $750,000.

The salaries for the seven-month period for Messrs. Snyder, Beeler, Rosen, K. Kelly, the stenographer and the technician will be about $5700. Professor Gathercoal will direct the Laboratory during the year and the honorarium due September 1st will be $750.00

Lists have been made of the ordinary laboratory glassware, bacteriological glassware and the usual non-permanent apparatus, reagent chemicals, U. S. P. and N. F. drugs and chemicals that will be needed in the Laboratory the first year, and the total cost of these in moderate quantities will not exceed $1000.

Traveling expenses for the Laboratory Committee and Chairman Gathercoal will total a considerable sum for the year. Under Miscellaneous we include the cost of gas and electricity, 3% unemployment tax on the salaries and probably a large number of other incidental items.

Finally, in the matter of research grants to other institutions, we should definitely set aside the interest from the A. PH. A. Research Fund for this purpose. The placement and supervision of the work under such grants in the future will be a most important duty of the laboratory director. This kind of work, when properly directed, yields very valuable results. We are placing as of January 1, 1938, a grant with the University of Illinois College of Pharmacy for $600.00, with Purdue University one for $400.00, with the Massachusetts College of Pharmacy one for $400.00 and with the University of Illinois College of Medicine one for $500.00. We have plans for placing grants with other institutions where specific N. F. problems are being undertaken all under the direct guidance of the chairman of the N. F. Committee for 1938. Other gifts made to the A. PH. A. for special research also should be handled through the A. PH. A. Laboratory.

In view of all of the statements made above, the following budget is recommended to the Council by the Laboratory Committee, to be added to the general budget of the ASSOCIATION for 1938:

Receipts.—It is understood by the Laboratory Committee that moneys available for the preparation, equipment and maintenance of the Laboratory during 1938 are to be or may be derived from the following sources:

Maintenance Fund	$20,000.00
N. F. Revision Fund	3,000.00
A. PH. A. Research Fund, for outside grants	2,500.00
Gift for a Special Research on Calomel Ointment	1,000.00
U. S. P. Contribution to the Color Research	750.00

It is expected that a further contribution to the Maintenance Fund for the equipment of the Laboratory, possibly amounting to $5000 will be available in whole or in part for the purchase of permanent apparatus prior to the removal of the Laboratory to Washington. Supplemental budgets will be submitted as required.

Disbursements.			
Permanent Investment.			
Item 1	Preparation of Nine Rooms for the Laboratory	$4000	
Item 2	Laboratory Furniture	6250	
Item 3	Office Furniture	500	
Item 4	Permanent Apparatus	350	$11,100
Maintenance Expenses.			
Item 5	Honorarium to March 1, 1938	750	
Item 6	Salaries to June 1, 1938	1700	
Item 7	Honorarium to September 1, 1938	750	
Item 8	Salaries, June 1 to December 31, 1938	5900	
Item 9	Supplies	1000	
Item 10	Traveling Expenses	750	
Item 11	Miscellaneous	500	$11,350
Special Research Grants.			
Item 12	From the A. PH. A. Research Fund	2500	2,500
	Total Disbursements		$24,950

(*Motion No. 11*) It is moved by Gathercoal that the Laboratory Budget as recommended by the Committee be approved with the understanding that if additional money comes in for equipment, Item 4, Permanent Apparatus, shall be increased to a sum equal to the amount received and not to exceed $4350, and that when the payment for the special research on Calomel Ointment is received it shall be considered as appropriated for that purpose, and be known as Item 13 of the budget.

(*Motion No. 12*) It is moved by Beal that Secretary Kelly be authorized on behalf of the A. PH. A. to enter into a contract with the Kewaunee Manufacturing Company for the preparation, delivery and installation, according to specifications, of the twenty-one specified articles of laboratory furniture at a price not over $6250.

(*Motion No. 13*) It is moved by Eberle that Secretary Kelly be authorized to enter into one or more contracts on behalf of the A. PH. A. to prepare the laboratory rooms for the installation of the furniture and at a total cost not to exceed $4000.

As it is necessary to get the preparatory work started promptly, a vote on these motions is called for at this time.

E. F. KELLY, *Secretary.*

LETTER NO. 6.

February 3, 1938.

34. Budget for 1938. Motion No. 7 (Council Letter No. 4, page 156) has been carried. $100.00 has been added to the appropriation for 1937 for Printing, Postage and Stationery and the budget for 1938 is approved as submitted. Dr. DuMez comments that further consideration of Item No. 30, JOURNAL, will be necessary later on account of the costs of the Proceedings Number, and Dr. Fischelis is recorded as not voting on this motion.

35. Selection of Auditor. Motion No. 8 (Council Letter No. 4, page 157) has been carried as W. A. Johnson, Baltimore, Md., is selected to audit the accounts for 1937.

36. Honoraria to Members of the Committee on National Formulary. Motion No. 9 (Council Letter No. 4, page 157) has been carried with Dr. Fischelis recorded as not voting.

37. Election of Members. Motion No. 10 (Council Letter No. 4, page 157) has been carried and applicants for membership numbered 151 to 167, inclusive, are declared elected.

38. Budget for A. Ph. A. Laboratory for 1938. Motion No. 11 (Council Letter No. 5, page 160) has been carried and the proposed receipts and disbursements are now incorporated in the general budget for 1938 (see item No. 34, page 160) with the latter bearing No. 33, Laboratory. In the mean time notice has been received that the U. S. P. Contribution to the Color Research for 1938 of $750.00 has been approved and is available.

39. Preparation of Rooms and Installation of the Furniture for the Laboratory. Motions Nos. 12 and 13 (Council Letter No. 5, page 160) have been carried and the contracts as authorized will be entered into as promptly as possible.

Since the plans for the Laboratory were submitted, it has been possible to make certain improvements in them which, it is expected, will also reduce the cost. The work on the preparation of the rooms for the Laboratory was begun on Monday, January 31st, under Chairman Gathercoal's supervision, and it is hoped that it can be completed within six weeks. The Kewaunee Manufacturing Company are checking final plans for the furniture which will be installed as promptly as possible after the preparation of the rooms is completed.

40. Contract for the Publication and Distribution of the Journal for 1938. The following communication has been received from Chairman DuMez of the Committee on Publications: "I have a majority of votes of members of the Publication Committee in favor of awarding the contract for the publication of the JOURNAL OF THE AMERICAN PHARMACEUTICAL ASSOCIATION to the Mack Printing Company. I, therefore, recommend that the contract for the publication of the JOURNAL OF THE AMERICAN PHARMACEUTICAL ASSOCIATION for the ensuing year be awarded to the Mack Printing Company of Easton, Pa., which firm again submitted the lowest estimate of the cost."

(*Motion No. 14*) It is moved by DuMez that the contract for the publication and distribution of the JOURNAL OF THE A. PH. A. for 1938 be awarded to the Mack Printing Company, Easton, Pa., on the basis of its bid.

41. Use of the Text of N. F. VI. The following communication has been received from Chairman DuMez of the Committee on Publications: "In response to your request of the 15th instant, it is recommended that permission be again granted P. Blakiston's Son & Co., Inc., to use portions of the text of the N. F. VI in the publication of the 6th edition of Youngken's Pharmaceutical Botany and that the usual fee be charged for this grant."

(*Motion No. 15*) It is moved by DuMez that P. Blakiston's Son & Co., Inc., be granted permission to use portions of the text of N. F. VI in the sixth edition of Youngken's Pharmaceutical Botany, with the customary acknowledgment and with the usual charge of $5.00.

42. Applications for Membership. The following applications, properly endorsed and accompanied with the first year's dues, have been received:

No. 168, Robert Cleo Stokes, 57 St. Margaret St., Charleston, S. C.; No. 169, H. M. Corbett, Creemore, Ont., Canada; No. 170, Dudley E. Hall, 102 W. John St., Bay City, Mich.; No. 171, Jack Emerson Babcock, Edgewood Arsenal, Edgewood, Md.; No. 172, Mrs. O. A. Wakefield, Sanford, N. Car.; No. 173, Roy E. Allen, Jordan Cove, Waterford, Conn.; No. 174, J. K. Attwood, 1024 Park St., Jacksonville, Fla.; No. 175, Frederick M. Scholl, 5822 N. 15th St., Philadelphia, Pa.; No. 176, Joseph Turkish, 931 Fox St., Bronx, N. Y. C.; No. 177, J. R. Adams, Medical College of S. Car., Charleston, S. Car.; No. 178, James C. Chilcott, The Maltine Co., New York, N. Y.; No. 179, Jose Polak, P. O. Box 24-24, Mexico, D. F., Mexico; No. 180, Manuel Kizirian, Pharmacien au L. S. B., Aleppo, Syria; No. 181, Lester Shapiro, 851 Michigan Ave., Buffalo, N. Y.; No. 182, Alfred W. Walker Higgins, Louisville College of Pharmacy, Louisville, Ky.; No. 183, Avery M. Holland, New Castle, Ky.; No. 184, Albert Threlkeld, 765 S. Western Parkway, Louisville, Ky.; No. 185, James J. Hamilton, 129 E. Gray St., Louisville, Ky.; No. 186, Willard W. Poole, 2691 Boston Blvd., W., Detroit, Mich.; No. 187, Orlie C. Evans, 6650 Clifton Ave., Detroit, Mich.; No. 188, Dean H. Fishbeck, 3205 Kendall, Detroit, Mich.; No. 189, Chalmer L. Figley, 2490 Blaine Ave., Detroit, Mich.; No. 190, Emmett M. Altshul, 27 Duncan Ave.,

Jersey City, N. J.; No. 191, Dorothy M. J. Michalec, 413 Tripoli St., N. S. Pittsburgh, Pa.; No. 192, Murle Brock, University, Miss.; No. 193, Milton A. Lesser, 255 Ocean Ave., Brooklyn, N. Y.; No. 194, Adolf Hamburger, 551 Fifth Ave., New York, N. Y.; No. 195, Albert F. Tice, 2027 Noble St., W. Lawn, Penna.; No. 196, Roy Kenneth Snyder, 7142 Luella Ave., Chicago, Ill.; No. 197, Earl P. Guth, Duquesne University, Pittsburgh, Pa.; No. 198, Ennis Dallas Sandberg, 3915 Eaton, Kansas City, Kans.; No. 199, Stanley P. Porter, Duquesne University, Pittsburgh, Pa.; No. 200, Otto B. May, 198 Niagara St., Newark, N. J.; No. 201, William Robert Collins, 7410 N. Damen Ave., Chicago, Ill.; No. 202, Tulio Miguel Cordero, 66 Queensberry St., Boston, Mass.; No. 203, Harold T. Hayashi, 1253 Nuuanu St., Honolulu, Hawaii; No. 204, Bernard Benedict Jatul, 813 Washington St., Stoughton, Mass.; No. 205, Lorenzo Joseph Pico, St. Peter's Hospital, Brooklyn, N. Y.; No. 206, Leon Milhauser, 90–19 Boulevard, Rockaway Beach, N. Y.; No. 207, Iuzuru Kikuchi, 1022 Kopke St., Honolulu, Hawaii, No. 208, Jean Elizabeth Orendorff, 2704 Farnam, Davenport, Iowa; No. 209, Horace Armand Allen, P. O. Box 1246, Missoula, Mont.; No. 210, Theodore A. Blackman, 443 Broadway, New York, N. Y.; No. 211, Harold Moskowitz, 190 Mortimer Ave., Rutherford, N. J.; No. 212, Geo. T. Lambert, 677 N. Preston St., Philadelphia, Pa.; No. 213, Saul Abraham Bell, 115 W. 68th St., New York, N. Y.

(*Motion No. 16*) Vote on applications for membership in the AMERICAN PHARMACEUTICAL ASSOCIATION.

E. F. KELLY, *Secretary.*

ANNOUNCEMENT BY THE U. S. P. ANTI-ANEMIA PRODUCTS ADVISORY BOARD CONCERNING LIVER PREPARATIONS CONFORMING TO U. S. P. STANDARDS.

When liver and stomach preparations were admitted to the U. S. Pharmacopœia, Eleventh Edition, it was recognized that these products presented a different problem, from the viewpoint of standardization, than any question previously before the Pharmacopœia.

As no ordinary methods for standardization or testing were available, an Advisory Board, made up of specialists in the treatment of anemia, was appointed. This Board established methods for determining the value of anti-anemia products, and the basis for a U. S. P. "unit of potency." They also issued forms for reporting evidence of clinical value and announced regulations for indicating the potency of U. S. P. products and for the wording of the labels.

On the invitation of the Board, a large number of clinical reports were submitted by manufacturers in evidence of the value of their products, and the Anti-Anemia Board, after reviewing these records, herewith submit their conclusions. This first report lists the products which have been approved up to this time as complying with the U. S. P. specifications and the firms authorized to sell or distribute them.

As is probably generally known, only a relatively small group of manufacturers have provided the necessary hospital facilities for checking the clinical value of anti-anemia products as required by the Board, and several of these distribute their products through the medium of other pharmaceutical firms.

Having been supplied with adequate clinical evidence of the efficiency of a manufacturer's product and having accepted it as of U. S. P. grade with a specific dose, the Anti-Anemia Board, on request has also authorized the distribution of some of these approved products by other firms when the firms have given assurance that their handling of the products will in no way alter its quality or potency. No doubt the Board will later report additional approved preparations and firms.

Report to be published in next issue of the JOURNAL.

E. FULLERTON COOK,
Chairman.

TEMPLE UNIVERSITY CONFERS DEGREES.

Mrs. Ruth Bryan Owen Rohde was the principal speaker at the exercises held February 15th, at which degrees in course were conferred upon 247 men and women, and honorary degrees were bestowed upon five distinguished Americans, including herself.

Honorary degrees conferred including: Mrs. Rohde, Doctor of Humane Letters; Dr. J. Leon Lascoff, president-elect of the AMERICAN PHARMACEUTICAL ASSOCIATION, Doctor of Science; Henry Butler Allen, secretary and director of the Franklin Institute, Doctor of Science; Dr. Murle M. Odgers, president of Girrard College, Doctor of Humane Letters; and Anthony J. Drexel Biddle, American Ambassador to Poland, Doctor of Laws.

EDITORIAL NOTES

PROBLEMS OF THE PHARMACOPŒIA.

In the January issue of the JOURNAL, page 5, "Problems of the Pharmacopœia" are discussed by *Chairman E. H. Wirth*, who would like to have more replies from interested persons on the subject. A reply, accordingly, was inserted on page XVI, of the *Advertising Section*, of the same issue of the JOURNAL, and it is hoped that more pharmacists will reply so that the Committee will be enabled to do this important work.

DANIEL HANBURY.
Face of Hanbury Medal.—see page 89.

Toronto, Canada.—A. E. Hanham, of Toronto. has been temporarily appointed secretary of the Canadian Pharmaceutical Association and editor of the organization's publication, the *Canadian Pharmaceutical Journal*. He succeeds Dr. R. B. J. Stanbury, who died recently.

Dr. George F. Bowerman, District of Columbia Librarian, presided at the last session of Bibliographers held in Washington, at the Library of Congress. Those who attended the meeting came from Latin America and an address was delivered by Raphel Heliodoro Valle, Professor of American history at the University of Mexico. His subject was "The Bibliographical Wealth of America."

DONATIONS.

William C. Powell, of Snow Hill, Maryland, has made several donations to the Museum of the AMERICAN INSTITUTE OF PHARMACY. A bell metal mortar was given to him by Dr. G. M. Vandergrift, of New York City. Mr. Powell was told this mortar was with the American soldiers at the Battle of Monmouth and Valley Forge—one of the Vandergrifts being surgeon. The other mortar, a Lignum Vitæ Mortar, was found under the "drifting sands" at Lewes, Del., and it is supposed to have belonged to the first president of the American Pilots' Association who was also a "dealer in spices."

Samuel L. Hilton has added to the list of magazines and books of the Library of the AMERICAN INSTITUTE OF PHARMACY.

F. W. Connolly, Boston, has donated a vial of grain musk and another Lignum Vitæ mortar and an unusual mortar and pestle; the latter is of particular interest because it covers completely the inside of the mortar and, doubtless, dates back to quite an early period.

Walter R. Brackenbury, M.P.S., Middlesbrough, London, England, sent with his compliments, the following books:

"Air Raid Precautions, Handbook No. 2"—"First Aid for Gas Casualties."

"Air Raid Precautions, Handbook No. 1"—"Personal Protection against Gas."

"Air Raid Precautions, Handbook No. 6"—"Air Raid Precautions in Factories and Business Premises."

"Air Raid Precautions, Handbook No. 4"—"Decontamination of Materials."

Published by His Majesty's Stationery Office, London, England.

Major General C. R. Reynolds, U. S. Army, Washington, D. C., has appointed **E. N. Gathercoal** a member of the Honorary Committee in connection with the Tenth International Congress of Military Medicine and Pharmacy, to be held in Washington, May 1939.

Liberty is taken in quoting the following two abstracts from the *Journal A. M. A.* of March 5, 1938:

Russell cites a fatal case of tetanus in a child of 18 months. The incubation period was twenty-four hours at the most and death ensued in about forty-four hours from the onset of the illness. The typical clinical signs were exhibited and large doses of anti-tetanus serum intramuscularly and intrathecally were given at the earliest opportunity. The sub-

sequent investigation seems to implicate a pigeon (or pigeons) as a "carrier" of tetanus. No animals were available for inoculation tests with the tetanus bacilli obtained on culture from the pigeon's droppings but the evidence otherwise would suggest the following chain of events: 1. The pigeon became infested with tetanus bacilli, probably by pecking horse manure, and became a "carrier," passing the bacilli or spores in its droppings, although showing no sign of illness itself. 2. The droppings infected the ground below the pigeon loft. 3. The child playing on the ground became infected through the skin, which was broken and scratched, as the result of active scabies. 4. The child developed clinical tetanus and died after a brief illness.

Bedson has prepared a psittacosis antigen from a crude virulent mouse-spleen suspension by centrifugating out the virus, resuspending it in phosphate buffer and heating the suspension for thirty minutes at 212° F. This heated antigen has been found superior to the crude virus suspension for carrying out complement fixation tests with the serums from patients with human psittacosis. The advantages of the heated antigen are that it makes the test more delicate, that it is not dangerous to handle and that it is stable.

PECTIN DERIVATIVE.

Dr. Edith Haynes, biologist, Indiana University, School of Medicine; Miss Grace Washburn, dietician, Dr. Charles A. Tompkins, and Dr. Matthew are quoted in a press dispatch on a pectin derivative as an antiseptic. The pectin used in these experiments came from citrus fruits—from the white inner layer of the fruit.

ESTIMATION OF SULFANILAMIDE IN BODY FLUIDS.

The author describes the method which is in use in the Wellcome Physiological Research Laboratories for determining sulfanilamide colorimetrically. The method is as follows: "One millilitre of blood, or body fluid, is diluted with 2 mils of distilled water; 1 mil of a 20 per cent aqueous solution of trichloracetic acid is then added, and the mixture filtered through a small filter-paper. To 1 mil of the filtrate is added 0.05 mil (one drop) of 0.05 per cent sodium nitrite solution. After three minutes 0.5 mil of a 1.0 per cent. alcoholic solution of dimethyl α-naphthylamine standing for fifteen minutes to allow the color to reach its maximum intensity, the color is compared with that containing known quantities of sulfanilamide. The comparison may be done in any of the usual forms of colorimeter. A range of permanent standards may be prepared using phenol red in phosphate buffer, or cobalt sulfate in dilute sulfuric acid."—H. Proom (*Lancet*, 1, 260 (1936)—through *The Pharmaceutical Journal*, page 211 (February 26, 1938)).

TERM "DRUG."

W. G. Campbell, Chief, Food and Drug Administration, U. S. Department of Agriculture, has issued the following statement regarding Venereal Disease Preventives:

"The Federal Food and Drugs Act defines the term 'drug' as including 'any substance or mixture of substances intended to be used for the cure, mitigation or prevention of disease.'"

Senator Morris Sheppard, Texas, attacked before a Senate committee a bill to permit the sending of eight-ounce "samples" of liquor through the mails. The House had already approved the measure but Sheppard declared the legislation would make the Government post-office "part of the liquor dealers" and render parents "powerless to prevent sending of liquor to minor children."

A Committee has been appointed by the A. PH. A. to collect Historical Data, composed of: Samuel S. Dworkin, *Chairman;* R. P. Fischelis and Robert L. Swain. Efforts will be directed to State and National Pharmacy and also made to enlist the interests of individuals and associations.

PURDUE UNIVERSITY HOLDS BUSINESS CONFERENCE.

The eighth annual Druggists' Business Bureau conducted each spring by Purdue University, will be held March 23rd–24th, and will be in charge of Prof. H. W. Heine.

He reports that plans for this year's Conference include such topics as "Correct Training," "Business Management," "Salesmanship Demonstration," "Traveling Aspects," "Social Security as It Affects the Druggists."

PERSONAL AND NEWS ITEMS.

J. B. Pilchard and **John L. Price** have opened a Prescription Pharmacy in Harrisburg.

John T. Lloyd, fellow member and son of our distinguished m. ber, the late John Uri Lloyd, has filed his application for incorporation of a pharmaceutical manufacturing company in Cincinnati, to be known as J. T. Lloyd Laboratories, Inc.

The directors of the new company, beside John T. Lloyd are William J. Miller and Attorney Francis Hoover.

Commander W. H. (M.C.) Michael, U. S. N. of the Army Industrial College is a member of the Committee of Arrangements for the International Congress of Military Medicine and Pharmacy to be held next year in Washington, D. C.

Dr. Perceval S. Rossiter, surgeon general of the U. S. Navy, and Capt. Harold Wellington Smith, in charge of the Naval Medical School, Washington, D. C., have been promoted to the rank of rear admiral in the naval medical corps. Surgeon General Rossiter has held this rank on a temporary appointment since 1933. He is a native of Shepherdstown, W. Va., and graduated at the University of Maryland School of Medicine, Baltimore, in 1895. Captain Smith graduated at the Harvard University Medical School, Boston, in 1901.

KILMER PRIZE TO MILTON KAHN.

Mr. Charles Schamach, chairman of the committee appointed by President Garrabrant in 1937, to judge the papers presented at our last annual convention in competition for the Dr. B. F. Kilmer Prize, reported that his committee had decided that the paper "Detailing the Physician," presented by Mr. Milton Kahn of Somerville at the 1937 Convention, was the most meritorious paper submitted. Chairman Schamach presented to Mr. Milton Kahn, the author of this paper, the Kilmer Award of twenty-five dollars. Mr. Kahn accepted with a very brief speech of thanks.

Morris Dauer, chief pharmacist of Kings County Hospital, Brooklyn, N. Y., has submitted his resignation as instructor in hospital pharmacy administration and management at St. John's University, College of Pharmacy, to take effect June 1st.

Mr. Dauer, who inaugurated the first course in hospital pharmacy administration and management in the history of academic pharmacy, at the time he became associated with St. John's in September 1936, plans to devote his leisure time in the future to develop more completely this course, and to completely prepare and make available a new and original course in public health pharmacy.

"There is an urgent need for well-trained hospital pharmacists and hospital pharmacy executives," Mr. Dauer declared. "Well-trained hospital pharmacists will be welcomed with open arms not only by federal, state and municipal hospital administrative executives, but also by the American community which will reap the benefits of their services."

J. Otto Kohl, prominent Cincinnati pharmacist, was honored at a testimonial dinner-dance which also celebrated his election to the executive committee of the National Association of Retail Druggists.

The testimonial was sponsored by his co-workers of several Associations and held in the Pavilion Caprice of the Hotel Netherland Plaza. Tributes came from President P. A. Schwarz of the State Association.

SPRING CLINIC AT UNIVERSITY OF BUFFALO.

Plans for the development of an annual "Spring Clinic" for licensed and practicing pharmacists have been announced at the University of Buffalo by Dean A. B. Lemon, of the School of Pharmacy. To inaugurate the new venture, a series of special lectures, demonstrations and discussions by outstanding authorities will be held on the University Campus on April 19th and 20th. All pharmacists of Western New York, whether alumni of the University of Buffalo or not, are invited to attend.

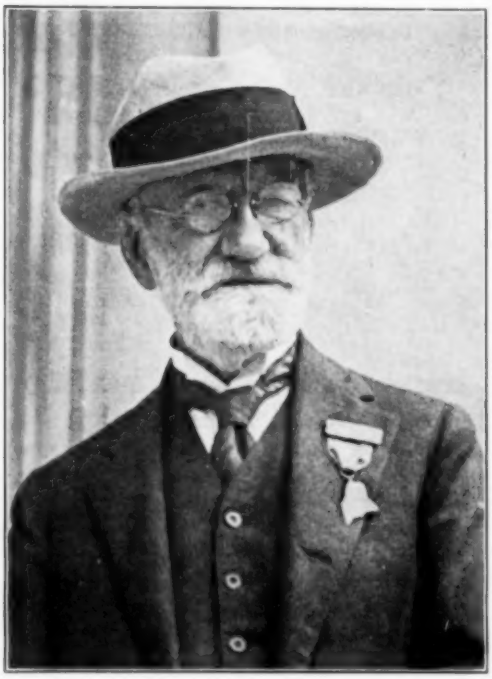
Secretary Russell B. Rothrock, of the Indiana Board of Pharmacy, has notified all package stores of the ruling of the Attorney-General's office, whereby such stores are ordered to cease the sale of all drugs except those medicines of secret composition which do not contain a poison or those which are especially exempted by statutes.

OBITUARY.

JAMES ALFRED SPALDING.

Dr. James A. Spalding, of Portland, Maine, *Honorary Member* of the AMERICAN PHARMACEUTICAL ASSOCIATION, died at his home February 27th, after a lingering illness, aged ninety-one years.

He was born at Portsmouth, N. H., in 1848, was graduated from Dartmouth College at the age of twenty, and received a Master's degree from Harvard Medical School when twenty-four. He studied abroad for three years, returning to Portland in 1873, to practice. He



DR. JAMES A. SPALDING.
Portland, Maine, Honorary Member, A. PH. A.

began specializing in eye and ear treatment and from 1881 to 1914 was ophthalmological and aural surgeon at the Main General Hospital; and became an outstanding specialist. He had been a consultant of the hospital since that time. He was the founder of eye and ear clinics at Augusta and Bangor, was awarded the degree of Doctor of Letters in 1928 by Dartmouth College, and was master of eleven languages.

At an honorary dinner in Portland in the summer of 1936, President Ernest M. Hopkins of Dartmouth lauded Dr. Spalding as "one of the most cultured gentlemen in New England." At that time Dr. Spalding responded by speaking in Irish and German.

Dr. Spalding was confined to the Maine General Hospital for two months in the winter of 1931–1932 as the result of a fall, but until recently was in excellent health for his advanced age.

He was a member of the American Ophthalmological Society, the American Academy of Medicine, the American Academy of Ophthalmology and Otology, the Maine Medical Association, of which he was once president, and the Cumberland County Medical Association. He was also a fellow of the American College of Surgeons.

With his late wife, the former Miss Sarah Chase Shepley, of Boston, whom he married in 1882, he took many trips to Europe, Egypt and Arabia.

He was the author of many articles for medical magazines and also wrote several books, including "Maine Physicians of 1820," and "The Life of Lyman Spalding."

Dr. Spalding was beloved in his home city and state and greeted his friends cordially and was a welcome visitor in their homes. When meeting those of foreign birth he pleased them by conversing with them in their mother tongue. He was a musician, despite his severe handicap, deafness; he had collected an extensive library and his home contained many pieces of art in pictures, literature and furnishings.

Dr. Spalding was a grandson of Dr. Lyman Spalding, the "Father of the U. S. Pharmacopœia." He had hoped to have a statue of him placed in the "Hall of Fame."

Surviving is a nephew, Merrill Spalding, of Palo Alto, Calif. The service, at Church, and flowers were very beautiful; the body of the deceased was laid to rest in Evergreen Cemetery beside that of his beloved wife.

The Northern Ohio Druggists' Association issues bulletins relating to coöperation of physicians and pharmacists. The purpose is to promote a mutual understanding by physicians and pharmacists, the promotion of better pharmaceutical practice to increase interest in the official medication of U. S. P. and N. F., to promote rational prescription writing, to correct the abuses of self-medication, to discourage the use of products of unknown composition and to reduce the cost of prescriptions.

FOOD AND DRUG BILL S. 5.

This Act may be cited as the Federal Food, Drug and Cosmetic Act J. 49855-1.

The term "drug" means (1) articles recognized in the official United States Pharmacopœia, official Homoeopathic Pharmacopœia of the United States, or official National Formulary, or any supplement to any of them; and (2) articles intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease in man or other animals; and (3) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (4) articles intended for use as a component of any article specified in clause (1), (2) or (3); but does not include devices or their components, parts or accessories.

Amend the title so as to read: "An Act to prohibit the movement in interstate commerce of adulterated and misbranded food, drugs, devices and cosmetics, and for other purposes."

Passed the Senate March 8 (calendar day, March 9), 1937.

The Act is well under way and more extended comment will be made when it becomes a law. It is to prevent the adulteration, misbranding and false advertisement of food, drugs, devices and cosmetics in interstate, foreign and other commerce subject to the jurisdiction of the United States, for the purposes of safeguarding the public health, preventing deceit upon the purchasing public and for other purposes.

The secretary shall promulgate regulations for the listing of coal-tar colors which are harmless. He is directed to promulgate regulations exempting labeling or packaging requirements. Provisions are made for a drug dispensed on a written prescription signed by a physician, dentist or veterinarian.

The Kansas State Pharmaceutical Association leads the state conventions; it is scheduled for March 21st-23rd at the Jayhawk Hotel in Topeka.

UNIVERSITY OF MISSISSIPPI.

Dr. Frank M. Huff, a member of the Biology Department faculty of the University, addressed members of the Pharmacy Club, using a four-reel moving picture in natural color to illustrate his talk. He spoke on "Biology of Florida and Cuba." More than thirty students and faculty members including Dean and Mrs. E. L. Hammond, Dr. and Mrs. W. W. Johnson and Mrs. Frank M. Hull, were present for the affair, which was sponsored by the local branch of A. PH. A. President B. V. Yelverton of the Pharmacy Club served as toastmaster.

BOOK NOTICES AND REVIEWS.

Handbook of Chemistry, by NORBERT ADOLPH LANGE, Ph.D. Lecturer in Organic Chemistry at Cleveland College of Western Reserve University; Member of the American Chemical Society, American Institute of Chemists and the Deutsche Chemische Gesellschaft; assisted by Gordon M. Forker, B.S., Harshaw Chemical Co., Cleveland, O.

A reference volume for all requiring ready access to chemical and physical data used in laboratory work and manufacturing, with an appendix of mathematical tables and formulas by Richard Stevens Burington, Ph.D., Assistant Professor of Mathematics at Case School of Applied Science.

This is the second edition, revised and enlarged, published by Handbook Publishers, Inc., Sandusky, Ohio. It contains 1800 pages including 250 pages of mathematical data and tables. The book is bound in fabri-coid and the price is $6.00. The extensive index indicates the comprehensive contents of 2500 listings covering 29 pages.

Among outstanding new features are the handling of hazardous chemicals; changes in atomic weights; organic reagents for inorganic analysis; laboratory solutions and special reagents for the industries. Favorable reviews have appeared in the publications of the latter.

Gould's Pocket Pronouncing Medical Dictionary. Tenth Edition. There are 40,000 words defined and pronounced in this Dictionary. In other words it is a Medical Dictionary in condensed form published by P. Blakiston's Son & Co., Inc., Philadelphia, Pa. To a large extent it provides the needs of the pharmacists, physicians, nurses, dentists and students. The issue has been revised up-to-date and a long list of dose tables has been included. The size of the book makes it possible to carry it in the pocket. The Dictionary has a flexible cover; the price of which is $2.00, and with the thumb index, $2.50.

Underhill. *Toxicology*, Third Edition. The Effects of Poisons. 325 pages. Washable cloth, $2.50. By FRANK P. UNDERHILL,

Ph.D. Revised by Theodore Koppanyi, Ph.D., Professor of Pharmacology and Materia Medica, Georgetown University Medical School.

Memoranda of Toxicology, by MAX TRUMPER, B.S., A.M., Ph.D., Consulting Clinical Chemist and Toxicologist. Member, United States Advisory Board of Hazardous Occupations for Minors. Formerly Lecturer on Toxicology, Jefferson Medical College, Philadelphia, Pa. Third Edition. Publishers, P. Blakiston's Son & Co., Inc., 1012 Walnut St., Philadelphia, Pa. Price, $2.00.

(*To be continued.*)

THE NEW HAMPSHIRE CRUISE.

Reference was made in January to the New Hampshire meeting of the State Pharmaceutical Association. President Moulton stopped in Washington before returning home from the District Meeting in Philadelphia and gave an interesting account of the trip. They were welcomed by Cuban pharmacists and the papers gave much publicity to the visit—the reporters were as ready with the cameras as here. The Cuban pharmacists were named as follows as visitors: Dr. Raul Romero Y Jordan, president; Dr. Juan E. Puig, past-president; Dr. Santos Buch, past-president; Dr. Jose P. Alacan; Dr. Enrique L. Triay; Dr. Jorge A. Dominicis; Dr. Moises Perez, vice-president; Dr. Francisco Hidalgo; Dr. Ricardo Galvez; Dr. Diego Mora, Havana delegate; Dr. Miguel Fernandes Garrido, past-president; Dr. Luis Ortiz; Dr. Agustin Ortiz y Planos; Dr. Angel Vieta; Dr. Atilano Soto; Dr. Pedro Bernal; Dr. Jose F. Meinecas; Dr. Jose Macias, vice-president; Dr. Idelfonso Bernal, treasurer; Dr. Eladio Gonzalez, vice-president; Dr. Alfredo Mazzuchelli, vice-treasurer.

Further references will be made.

THE AMERICAN DRUGGISTS' FIRE INSURANCE COMPANY.

The Directors and Stockholders of the A. D. F. I. Company held their Annual Meeting in Cincinnati on February 14th–16th. Nearly all of the 30,000 shares of the stock of the Company were represented at the meeting in person or by proxy.

James H. Beal, who among a life-time of activities in the interest of pharmacy and of the retail drug trade had also taken part in the organization of the A. D. F. I. Company thirty-two years ago, was elected the *President* of the Company. He had also served on its Executive Committee for thirty-two years and was its vice-president for many years. G. C. Young of Buckhannon, West Virginia, who has been a director and Executive Committee Member since 1907, was elected *Vice-President*. P. J. Suttlemyre, the president of the North Carolina Pharmaceutical Association, who had served on the Board of Directors for many years, and Joseph A. Hottinger of Chicago, Illinois, were respectively elected to the Executive Committee and to the Board of Directors to fill the vacancy caused by the death of Mr. Avery. All the other Officers of the Company, Members of the Executive Committee and Board of Directors were reëlected. The officers are: J. H. Beal, Cocoa, Florida, *President;* G. O. Young, Buckhannon, West Virginia, *Vice-President;* Walter Rothwell, Hatboro, Pa., *Treasurer;* E. H. Thiesing, Cincinnati, *Assistant Treasurer;* W. P. Starkey, Cincinnati, *Assistant Secretary;* Frank H. Freericks, *General Manager* and *Secretary*. The Executive Committee includes besides the president and secretary, Dr. William C. Anderson of New York, G. O. Young of West Virginia, Walter Rothwell of Pennsylvania, J. S. Rutledge of Akron, O., and P. J. Suttlemyre of North Carolina.

VITAMINS IN MODERN ASPECTS OF NUTRITION.

It is not so very many years since the science of nutrition was concerned solely with the caloric value and tissue-building properties of foods. Carbohydrates, proteins, fats, mineral salts and water were believed to supply all the needs of the animal and human body, and the task of dietitians was thought to be complete when they had provided these components of a diet in properly balanced proportions. Within the last two or three decades has come what appears to be the full recognition of the part played by vitamins in the prevention of ill-health, and this aspect of nutrition has proved to be a very lucrative form of appeal to the public imagination. One by one the vitamins are being isolated in pure form, and some have been synthesized.